Arthritis Advisory Committee

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NDA 20-998 Celebrex™ (celecoxib) Searle

Volume I: FDA Medical Reviews

Pain

Statistical Review

STATISTICAL EFFICACY AND SAFETY REVIEW

ALL ACUTE PAIN STUDIES

NDA:	**20-998**
Drug Class:	**Analgesic and Anti-inflammatory Agent**
Name of Drug:	**Celecoxib (SC-58635) [Celebrex] Capsules 100 mg and 200 mg**
Applicant:	**G.D. Searle** **4901 Searle Parkway, Skokie, IL 60077** **Contact: Winifred Begley (847) 982-8155**
Indications:	**Management of Acute and Chronic Pain;** **Treatment of Signs and Symptoms** **Of Osteoarthritis and Rheumatoid Arthritis**
Controlled Clinical Studies:	**Pain - N49-96-02-005; -025; -027; -028; -029; -070; -080** **Separate Review: RA-012; RA-022; RA-023; RA-041; OA-013; OA-020; OA-021; OA-042; OA-047; OA-054; OA-060; OA-087; GI-062; GI-071**
Statistical Reviewer:	**Lillian Patrician, MS, MBA**
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I. Background

On March 13, 1995, the sponsor began a clinical development program to investigate the efficacy and safety of SC-58635 Celecoxib as compared to placebo in the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis, and in the management of pain. Nonsteroidal anti-inflammatory drugs (NSAIDS) were included as positive control. The NDA was filed June 29, 1998. This drug has not been approved elsewhere in the world.

SC-58635 Celecoxib is a new molecular entity that is an analgesic and anti-inflammatory agent. It selectively inhibits cyclooxygenase-2 (COX-2), thereby reducing the formation of prostaglandins that are involved in inflammation. NSAIDS are the currently used analgesic and anti-inflammatory agents, referred to as COX-1 agents. They have a recognized degree of adverse effects including upper gastrointestinal (UGI) mucosal injury, impairment of renal function, exacerbation of hypertension, and alteration of platelet function.

This review is an evaluation of the performance of Celecoxib (Celebrex) as studied for the management of acute pain in studies using postsurgical pain models. A total of 1,347 patients with postsurgical pain were randomized to seven placebo-controlled clinical trials of up to five days treatment duration (Studies N49-96-02-005; 025; 027; 028; 029; 070; and 080).

Measurements of analgesic efficacy included time-specific pain assessments of Pain Intensity Difference or Change from Baseline (PID), Pain Relief (PR) and Sum of Pain Intensity Difference and Pain Relief (PRID), as well as Median Time to Perceptible Pain Relief.
[Attachment # 1 - Page 25]

The analgesic effect on pain experienced by Osteoarthritis and Rheumatoid Arthritis patients was evaluated under separate statistical review for studies conducted for the treatment of the signs and symptoms of OA and RA (OA studies -020; -021; -042; -047; -054; -060; -087, and RA studies -022; -023). During a Pre-NDA meeting on 12-FEB-98 between the FDA and sponsor, the concept of a general chronic pain claim was discussed. A chronic pain claim and the types of studies needed to support such a claim was not determined. The sponsor planned to propose a labeling with the NDA.

II. Overall Safety Summary in Acute Pain Studies *[Attachments # 2 A-B-C - Pages 26-28]*

1. Patient Disposition: There were 1,347 patients enrolled in the six acute pain studies, 005, 025, 027, 028, 029, and 070 in which 305 were randomized to placebo, and 294 to active control agents: 50 to Ibuprofen 400 mg; 50 to Aspirin 650 mg; 89 to Naproxen 550 mg; and 105 to Darvocet 100 mg. There were 748 Celecoxib patients: 50 were in the 25 mg; 85 in the 50 mg; 268 in the 100 mg; 260 in the 200 mg; and 85 in the 400 mg dosage groups. Nine hundred fifty-four (954) or 71% of the patients were Caucasian; 257 or 19% were Hispanic; and the remaining 136 or 10% were of other racial origins. More females than males participated; 816 or 61% were female and 531 or 39% were male. *[Attachment # 2A - Page 26]*

2. Safety Profile: The overall safety profile for Celecoxib use in these short-term acute pain studies was comparable to placebo and the positive control agents. Throughout all acute pain studies, no deaths and no serious adverse experiences were reported. Nine hundred twenty-five (925) or 69% of the patients completed study by definition of "completion" established in the study reports. Across treatment groups, a comparable percentage of patients discontinued due to adverse reactions: placebo (3%); Celecoxib groups (2%); and active comparator agents (2%). More placebo patients discontinued due to treatment failure (26%) as compared to Celecoxib (20%) and active control agents (22%). However, fewer placebo patients discontinued for reasons of noncompliance (3%) as compared to Celecoxib (6%) and active control (11%).

3. Adverse Reactions: Seven Hundred ninety-five or 59% of the patients had no concurrent adverse experiences. Five hundred fifty-two (552) or 41% reported reactions: 124 or 9% noted at least one severe reaction; 255 or 19% had no higher than moderate reactions; and 173 or 13% had no higher than mild. By the investigators' opinions regarding relation to treatment, 17 or 1% of the patients had adverse reactions that were considered probably related, and 301 or 22% were patients whose relation to drug was deemed uncertain. The sponsor included a secondary review of these adverse experiences and determined according to their medical opinion that 248 or 18% of the patients had adverse reactions that were related to treatment.

The percentage of patients reporting reactions was comparably distributed among treatment groups. While 40% of placebo patients reported adverse experiences, 41% of all Celecoxib patients did so, and 43% of the patients in the active control groups also reported adverse experiences. There was also a comparable distribution of patients experiencing severe adverse reactions: 10% of placebo patients; 9% of Celecoxib patients; and 11% of active comparator patients reported severe adverse reactions.

Five hundred fifty-two (552) of the 1,347 patients enrolled in the acute pain program reported a total of 995 adverse reactions. The incidence of reaction per patient was higher in the active comparator group. Two hundred fourteen (214) reactions were experienced by 305 placebo patients resulting in 0.70 reactions per patient, and a comparable 0.71 for the 531 experiences reported by the 748 Celecoxib patients. However, the 294 active control patients taken as a group reported 250 reactions resulting in 0.85 reactions per patient.

The highest incidence of reactions was nausea; headache; alveolar osteitis; vomiting; and dizziness. Celecoxib patients had a lower percentage incidence of nausea (12%) than those taking active control agents (16%), although both groups were higher than placebo (8%). Celecoxib patients also had a lower percentage incidence of headache (8%) compared to active control (12%) and placebo (13%). However, the percentage incidence of alveolar osteitis was higher in the Celecoxib group (8%) than in active control (5%) and placebo (6%). There was comparable percentage incidence of vomiting (5% to 6%) and dizziness (4% to 5%) in all three treatment groups. There was also a comparable incidence of severe adverse reactions reported across the placebo (11% of all reactions were severe), Celecoxib (12% were severe), and active comparator groups (14% were severe). There was no prevalence of specific adverse reaction per sex or racial group. ***[Attachment # 2B - Page 27]***

Patients in the Celecoxib group and not those in the placebo and active control groups experienced a low incidence of certain adverse reactions. These are noted in the event that they may represent a safety signal regarding use of this investigational drug. They include reports of anxiety; arthrosis; asthenia; epistaxis; fatigue; hypokinesia; ileus; influenza-like symptoms; LDH increase; menorrhagia; pallor; pneumothorax; abnormal stools; stupor; and vasodilation. Additionally, even though the incidence rate is again very low, there was a higher incidence of confusion; diarrhea; dyspepsia; hot flushes; oral hemorrhage; somnolence; and upper respiratory tract infection reported by patients in the Celecoxib group than by placebo and active control. ***[Attachment # 2C - Page 28]***

III. Protocol Considerations

1. Intent-to-Treat Analysis (ITT): The sponsor analyzed all pain management studies by using an ITT Cohort defined as "all randomized patients (with two exceptions) who took at least one dose of study drug. One exception was exclusion from the efficacy analysis for patients who required rescue medication prior to the one-hour assessment. Additionally, if two consecutive scheduled pain assessments in the first two hours were missed, and therefore obtained by interpolation from the same two observed data points for any patient, that patient was excluded from the analyses". Time-specific pain measurements were analyzed at all defined time points.

2. Missing Values: As per the 12-FEB-98 Pre-NDA meeting, the sponsor decided to consider 2 approaches to missing values, that of using both the LOCF (last observation carried forward) and BOCF (baseline observation carried forward) for imputing pain intensity and pain relief data after the patient took rescue medication.

3. Measures of Analgesic Efficacy in Post-surgical Pain Studies: Time-Specific Pain Intensity (Categorical) was assessed as pain at this time is 0=none; 1=mild; 2=moderate; 3=severe. Time-Specific Pain Relief (PR) assessed by relief from starting pain of 0=none; 1=little; 2=some; 3=lot; 4=complete. Time to Rescue Medication was calculated as the difference between the start time for the rescue medication and time the first dose was taken.

Time to Onset of Perceptible Pain Relief (Studies 025, 027, 070 only) was assessed by instructing the patient to click a stopwatch at the time of perceptible pain relief. Each patient was instructed: "I would like you to stop the stopwatch when you first feel any pain-relieving effect whatsoever from the drug. This does not necessarily mean you feel completely better, although you might, but when you first feel any differences in the pain that you have had."

Time-Specific Pain Intensity (VAS) was assessed by asking the patient to place a mark on the 100 mm VAS [ranging from 0 mm (no pain) to 100 mm (worst pain)] to indicate pain magnitude.

Time to Onset of Meaningful Pain Relief (025, 027, 070 only) was assessed by instructing the patient to stop a stopwatch at the time when he or she first experienced meaningful pain relief. Each patient was given the following instruction: "I would like you to stop the stopwatch when you have meaningful pain relief. That is, when the relief from the pain is meaningful to you."

4. Primary Efficacy Measures:
   1) Time-Specific Pain Intensity Difference (PID) (Categorical), derived by subtracting from the Baseline pain intensity score the pain intensity score at the post-dose time points (emphasis in the ISE at the time points up to eight hours). Time-Specific Pain Intensity was assessed as a categorical scale of 0=none; 1=mild; 2=moderate; 3=severe.
   2) Time-Specific Pain Relief (PR), measured at the post-dose time points (emphasis in the ISE at the time points up to eight hours). Time-Specific Pain Relief (PR) was assessed as 0=none; 1=little; 2=some; 3=lot; 4=complete.
   3) Time-Specific Sum of PID on categorical scale and PR (PRID), at the post-dose time points (emphasis in the ISE at the time points up to eight hours);
   4) Time to Onset of Perceptible Pain Relief.

Mean Pain Intensity Difference and Pain Relief (PRID) Scores were calculated as the sum of the Pain Relief (PR) Score and Pain Intensity Difference (PID) Score. The best possible score was 7 (complete pain relief [PR=4] and change from severe pain at Baseline to no pain [PID=3]. The worst possible score was -1 (no pain relief [PR=0] and change from moderate pain at Baseline to severe pain [PID= -1]). Mean Pain Relief (PR) scores were reported on a scale of 0 to 4 with 0 indicating no pain relief and 4 indicating complete pain relief. Mean PID (Categorical) Scores were calculated by subtracting the pain intensity at a specific assessment time from the Baseline pain intensity. Scores could range from -1 (worst possible score) to 3 (best possible score).

5. Secondary Efficacy Measures:
   1) Time-Specific Pain Intensity Difference (VAS), derived by subtracting from the Baseline pain intensity score, the pain intensity score at the post-dose time points;
   2) Summed Pain Intensity Difference, (SPID), for the sum of the PID scores through the first 3, 6, 8, 10 and 12 hours, respectively;
   3) Total Pain Relief (TOTPAR) for the sum of the PR through hours 3, 6, 8, 10 and 12;
   4) Summed PRID scores (SPRID) for the sum of the PRID scores through the first 3, 6, 8, 10 and 12 hours, respectively;
   5) Time to First Experienced 50% Pain Relief;
   6) Proportion of patients who experienced 50% pain relief;
   7) Proportion of patients who experienced 100% pain relief defined as complete pain relief (PR=4) and pain intensity (categorical) rating of none (PI=0).

6. Statistical Assessment of Efficacy Variables: The sample size calculation was based on one primary efficacy variable (PID), and the comparison of each dose of Celecoxib versus

placebo. A sample size of 50 patients per treatment group was required to detect with at least 80% power and type I error at 0.0167 (for a two-sided test adjusted for three comparisons) a difference of at least 0.396 at 45 minutes in the PID score. The estimate of variability used for sample size calculations in the PID scores at 45 minutes is 0.60.

A one-way analysis of variance (ANOVA) was performed to determine whether the randomization was successful in creating treatment groups that exhibited only chance variations at Baseline with respect to age, height, weight, and vital signs. Homogeneity of treatment groups in terms of gender and race was examined by Pearson's Chi-square test. The summary of dental surgery and Baseline data (categorical variables including surgical trauma rating, maximum degree of impaction, Baseline pain intensity, and number of molars extracted) were analyzed with Pearson's Chi-square test. Other Baseline variables included the time from surgery until taking study medication, and the Baseline pain intensity (VAS). These variables were analyzed using ANOVA. Number of molars extracted was also analyzed using ANOVA.

Time-specific PID (Categorical and VAS), time-specific PR, time-specific PRID, SPID, TOTPAR, and SPRID were analyzed using ANOVA with treatment and patient's pain intensity at Baseline as factors. For time-specific PR, the analysis was also performed without patient's pain intensity at Baseline included as a factor. The Baseline pain intensity was treated as a categorical variable except for PID (VAS) where pain intensity at Baseline was treated as continuous. A p-value was provided for the treatment effect with treatment and Baseline being the factors in the ANOVA model. For subgroup analyses, a p-value provided age and gender effect by including these separately in the ANOVA model. Fisher's protected least significant difference (LSD) multiple comparison was applied to the model-adjusted treatment means.

Time to Onset of Perceptible Pain Relief, Time to Meaningful Pain Relief, Time First Experienced 50% Pain Relief and the Time to Rescue Medication were analyzed using survival analysis methods. The median time to event for each drug group was calculated using the Kaplan-Meier product limit estimator. Ninety-five percent confidence intervals on the median time to event were calculated using the method of Simon and Lee. An overall log-rank test comparing treatment groups was performed. If the overall test was significant, pairwise comparisons were made between treatment groups using pairwise log-rank tests as outlined below: For time to event variables: Time to Onset of Perceptible Pain Relief, Time to Meaningful Pain Relief, Time First Experienced 50% Pain Relief, if a patient took rescue medication before experiencing the event, the time to event variable was set to take an event time equal to 24.1 + (0.005 Time to Rescue Medication) hours. The shorter the time to rescue, the longer the time to event.

For the Analysis of Post-General and Post-Orthopedic Surgery Studies, the single dose (Day 1) data were carried out in a manner analogous to that used in the single dose post-oral surgery studies. These analyses were based on the pain assessments before first remedication or rescue medication. The multiple dose data were analyzed and based on the pain assessments before rescue medication using similar statistical methodology.

Time to Onset of Perceptible Pain Relief and Meaningful Pain Relief Calculation: If a patient stopped the first stopwatch, then that time was taken as the Time to Onset of Perceptible Pain Relief. If a patient stopped the second stopwatch, that time was Time to Meaningful Pain Relief. If the patient stopped only the first stopwatch, and did not take rescue medication, Time to Meaningful Pain Relief was taken as a censored time equal to the lesser of 24 hours or the time to withdrawal. If the patient took rescue and stopped only the first stopwatch, then the Time to Meaningful Pain Relief was taken as an event time equal to 24.1 + (0.005 ÷ Time to Rescue Medication) hours. If the patient stopped neither stopwatch and did not take rescue medication,

the Time to Onset of Perceptible Pain Relief and Time to Meaningful Pain Relief were taken as a censored time (24 hours or the time to withdrawal). If the patient took rescue and stopped neither stopwatch, the Time to Onset of Perceptible Pain Relief and Time to Meaningful Pain Relief were taken as an event time equal to 24.1 + (0.005 ÷ Time to Rescue) hours.

Time First Experienced 50% Pain Relief: For patients not experiencing 50% pain relief and who took rescue medication, the Time to First Experienced 50% Pain Relief was taken as an event time equal to 24.1 + (0.005 ÷ Time to Rescue Medication) hours. For patients not experiencing 50% pain relief and who did not take rescue medication, this time was taken as the lesser of 24 hours or the time to withdrawal. The percentage of patients with at least 50% pain relief was analyzed by pairwise Fisher's exact test.

IV. Pain Study 005 - Postsurgical Dental Pain *[Attachment # 3 - Page 29]*

1. Study Design: Study 49-96-02-005 was a Phase 2, single-blind, placebo-controlled comparison of the safety and efficacy of 2 doses of Celecoxib (100 and 400 mg) with Placebo and Aspirin 650 mg in patients with moderate to severe postsurgical dental pain following extraction of third molar teeth (one of which must have been mandibular) requiring bone removal.

The study was conducted between 08/23/95 and 10/03/95. The protocol date is 6/22/95.

Amendment #1, dated 8/4/95, changed the comparator in the study from Ibuprofen to Aspirin.

Administrative Change #1, dated 8/14/95, reconciled data collection on the case report forms with the Searle database; and Administrative Change #2, dated 10/25/95 (almost 1 month after end-of-study), modified the statistical sections of the protocol to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1995) as recommended by the FDA Pilot Drug Evaluation Staff.

The sponsor's study report was revised in 12/97 after end-of-study for the following changes:
1) The definition of a patient who completed the study was changed from one who completed evaluations through 1 hour (as defined by protocol), to one who completed through 24 hours; and
2) The method of extrapolation for pain scores was changed to be consistent with the FDA draft guidance document (Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models, Jan 1997) and with other analgesia studies conducted in the program. This change in methodology resulted in slight differences in the efficacy results.

There was a Pretreatment Visit, Surgical Procedure, a Baseline Visit, a 24-hour Treatment Period, and a Post-treatment Period. The Pretreatment Visit occurred within 14 days prior to the administration of study medication. At the Surgical Procedure, the molar(s) was extracted and an oral surgeon made a surgical trauma rating. At the Baseline assessment, only patients experiencing moderate to severe pain (greater than or equal to 50 mm on a VAS of 100 mm) within six hours of the completion of surgery were enrolled into the study.

The Treatment Period was the 8-hour period immediately following the administration of a single dose of study medication. Patients remained in the research unit for the 8-hour Treatment Period. Scheduled pain assessments were at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post-dose. Assessments included Pain Intensity (Categorical Scale); Pain Relief; Pain at Least Half Gone; Pain Intensity (VAS); and Patient's Global Evaluation.

The use of potentially confounding medications in the post-surgical period was restricted as specified in the protocol. Patients were allowed to take rescue medication at any time in the study, if needed. Prior to taking the rescue medication, the patients completed a final pain assessment and were dropped from the study. For those patients who did not take rescue medication, the final pain assessments and end-of-study safety assessments were performed in the Post-treatment Period.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. For all patients, the age range was Across treatment groups, of the patients were male and were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.966$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.612$, continuous). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.069$). Mean pain intensity across treatment groups was and mean time until taking study medication was after surgery.

3. Sponsor's Evaluation: The sponsor reports, "The single Celecoxib doses of 100 and 400 mg were effective analgesic agents in the dental pain model; they were safe and efficacious in alleviating post-oral surgery pain. A nonefficacious dose was not identified. Based on these results, doses of 25 mg, 50 mg, 100 mg, 200 mg and 400 mg were studied in Phase III trials." *[ISE - Page 339 of 355]*

Fisher's protected LSD multiple comparison procedure was applied to the adjusted treatment means. The time to rescue medication was analyzed by pairwise log-rank tests. Patients not requiring rescue medication were considered censored at eight hours for the time to rescue medication analysis. The above pairwise multiple comparisons were done in the same fashion as Fisher's protected LSD. This means an overall log-rank test on the time to rescue medication was performed. If the overall test was significant, pairwise comparisons were made between the treatment groups using pairwise log-rank tests.

4. Reviewer's Evaluation: This single-blind study did not undergo a full efficacy review. The treatment medications were dispensed as bottles of 4 capsules for the placebo, 100 mg and 400 mg arms, and as bottles of 2 Nuprin caplets plus 2 placebo capsules for the positive control arm. Therefore, the secondary objective, "to compare the analgesic activity of aspirin 650 mg versus placebo in patients with moderate to severe pain in a postsurgical dental pain model and to assess the relationship between SC-58635 plasma concentrations and pain intensity difference (PID) scores 1 hour post-treatment" was not met under fully blinded conditions.

However, the sponsor's analyses indicate that both 400mg and 100mg SD Celecoxib groups showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF in both dosage groups, statistically superior mean Pain Relief (PR) and mean Pain Intensity Difference (PID) began 45 minutes postdose and continued through Hour 8. Positive control Aspirin 650mg was superior to placebo beginning 30 minutes postdose through Hour 8; to Celecoxib 400mg beginning 30 minutes postdose through Hour 1; and to Celecoxib 100mg beginning 45 minutes postdose through Hour 8.

V. Pain Study 025 - Postsurgical Dental Pain *[Attachment # 4 - Page 30]*

1. Study Design: Study 49-96-02-025 was a double-blind, placebo-controlled comparison of the safety and efficacy of 3 single doses (SD) of Celecoxib (25, 50, and 200 mg) with Placebo and Ibuprofen 400mg SD in patients with moderate to severe postsurgical dental pain following extraction of molar teeth involving mandibular bone removal. This study followed the same design and included the same patient population as that of Study N49-96-02-005, however, the study was double-blind and of 24-hour duration. Scheduled pain assessments were made at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. Additionally, patients were given 2 stopwatches to separately record Time to Perceptible and Time to Meaningful Pain Relief.

The study was conducted from 7/9/96 through 11/7/96. The protocol date is 6/3/96. One amendment is dated as 6/13/96. The sponsor's study report was revised after the end-of-study in 12/97 for the following: (1) The definition of a patient completing study was changed from completing evaluations through 1 hour (as defined by protocol), to completing through 24 hours; (2) The method of extrapolation for pain scores was changed to be consistent with the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1997) and with other analgesia studies conducted in the SC-58635 program. This change in methodology resulted in slight differences in the efficacy results. (3) Adverse events were recoded for consistency with other reports in the program.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. For all patients, the age range was Across treatment groups, of the patients were male and were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.217$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.927$, categorical and $p=0.756$, continuous). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.281$). Mean pain intensity across treatment groups was and mean time until taking study medication was after surgery.

3. Sponsor's Evaluation: The sponsor reports, "Celecoxib 25 mg and 50 mg were submaximally efficacious doses in Study 025 as higher doses of Celecoxib were associated with a greater degree of analgesic efficacy." It was also reported, "Across all efficacy measures there was a statistically significant increase in analgesic effectiveness with increasing doses of Celecoxib, with the 200 mg dose level providing the most rapid relief with the longest duration as compared to the Celecoxib 50 mg, 25 mg and placebo treatments". *[ISE - Page 339 of 355]*

"The results of this study demonstrate that, for all primary (PID, PR, PRID, Time to Onset of Perceptible Pain Relief, Time to Rescue Medication) and secondary (Time-Specific PID VAS, PPID, Peak Pain Relief, Time to Meaningful Pain Relief, Time to 50% Pain Relief, Percent of Patients Experiencing at Least 50% Pain Relief, Patient Global Evaluation, and the 6, 8,10, 12, and 24 hour SPID, TOTPAR, and SPRID) measures of efficacy, single oral doses of SC-58635 at dose levels of 25 mg, 50 mg and 200 mg provided greater relief from moderate to severe postoperative dental pain than placebo."

"Across all efficacy measures there was a statistically significant increase in analgesic effectiveness with increasing doses of SC-58635, with the 200 mg dose level providing the most

rapid relief with the longest duration as compared to the SC-58635 25 mg, 50 mg and placebo treatments. The SC-58635 200 mg dose level demonstrated greater analgesic efficacy as compared to the SC-58635 25 mg, 50 mg and placebo treatments. This greater analgesic efficacy persisted throughout the 24 hour Posttreatment Period".

"This difference in analgesic response was consistently numerically better than placebo for most assessment times after 0.5 hours postdose and was statistically significant for the SC-58635 200 mg dose as compared to placebo for all the summed efficacy measures at all assessment times. The increase in SC-58635 200 mg analgesic efficacy was also statistically significant for PID (1.0-24.0 hours), PR (0.75-24.0 hours), PRID (0.75-24.0 hours), and percent of patients experiencing at least 50% Pain Relief The SC-58635 200 mg dose level provided statistically significant more rapid onset of Time to Perceptible Pain Relief".

4. Reviewer's Evaluation : ***[Attachment # 9 A-B - Pages 37-38]*** A repeated analysis of primary efficacy parameters using the sponsor's efficacy datasets for LOCF verified the results reported in the submission. These were again executed after modifying for baseline-observation-carried-forward (BOCF). The results for LOCF offer Celecoxib a slightly better advantage over those for BOCF primarily in that the duration of statistical significance is longer for LOCF than BOCF. ***[Missing Values - Page 3]***

Celecoxib 200mg SD demonstrated analgesic efficacy compared to placebo when used in a postsurgical dental pain model. Using LOCF, statistically superior mean Pain Relief (PR) beginning 45 minutes postdose (p=0.0173) through Hour 24 (p= 0.0004). Mean Pain Intensity Difference (PID) began 1 hour postdose and continued through Hour 12. The Celecoxib 25mg and 50mg dosage levels also separated from placebo for these 2 efficacy measures, but the superiority only lasted for 2 hours duration. Ibuprofen 400mg, used as a postive control, demonstrated superiority to placebo from 45 minutes (p=0.0001) through Hour 11 (p=0.0398), and also to the 3 dosage levels of Celecoxib at varying assessment timepoints.

Using BOCF, statistically superior mean Pain Relief (PR) for the Celecoxib 200mg group compared to placebo began 45 minutes postdose and continued through Hour 10. The mean Pain Intensity Difference (PID) began 1 hour postdose and continued through Hour 9. The Celecoxib 25mg and 50mg dosage levels also separated from placebo for these 2 efficacy measures, but the superiority only lasted for 2 - 4 hours duration. Ibuprofen 400mg was superior to placebo from 45 minutes postdose through Hour 8 (PR) and Hour 9 (PID), and also to the 3 dosage levels of Celecoxib at varying assessment timepoints.

Mean Pain Intensity Difference (PID-LOCF) ***[Study Report Table 025-9 - Pages 39-41]*** or change from baseline for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 1 and continuing up to Hour 3 following treatment. The 200mg and 50mg groups continued with statistically significant differences through Hour 12. At 45 minutes, 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Mean Pain Relief (PR-LOCF) ***[Study Report Table 025-10 - Pages 44-46]*** for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 1 and continuing up to Hour 3 postdose. The 200mg SD group showed a statistically significant difference beginning 45 minutes after treatment start and

continuing through Hour 24. At 45 minutes, positive control 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 3, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Only patients in the Ibuprofen 400mg SD group achieved a meaningful level of analgesia (74% of Ibuprofen 400mg patients compared to 18% of placebo; 42% of 25mg; 46% of 50mg; and 54% of 200 mg Celecoxib patients). A higher percentage of Ibuprofen patients also achieved a perceptible level of pain relief (82% of Ibuprofen 400mg patients compared to 36% of placebo; 58% of 25mg; 64% of 50mg; and 70% of 200 mg Celecoxib patients). ***[Study 025 App 2.3]***

Mean Sum of Pain Intensity Difference and Pain Relief (PRID-LOCF) ***[Study Report Table 025-11 - Pages 49-51]*** in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo beginning at Hour 0.75 and continuing up to Hour 10 following treatment. The 200mg group continued with statistically significant differences through Hour 24. At 45 minutes, positive control 400mg SD Ibuprofen was statistically superior to all levels of Celecoxib, as well as placebo. Ibuprofen remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and numerically superior to Celecoxib throughout the subsequent hourly assessments.

Median Time to Onset of Perceptible Pain Relief - LOCF ***[Study Report Table 025-12 - Pages 53-54]*** for patients in all 3 Celecoxib dosage groups (25, 50, and 200 mg SD) showed a statistically significant difference from placebo. The positive control, 400mg SD Ibuprofen, was statistically superior to the 50 mg and 25 mg levels of Celecoxib, as well as placebo. The median time to onset was 0:33 for Ibuprofen; 0:38 for Celecoxib 200mg; 1:05 for Celecoxib 50mg; 0:53 for Celecoxib 25mg; and >24:00 for placebo.

Median Time to Administration of Rescue Medication - LOCF revealed that fewer patients in the 200mg Celecoxib group required rescue medication than in any other treatment group, including Ibuprofen (84% of Ibuprofen 400mg compared to 92% of placebo; 92% of 25mg; 86% of 50mg; and 74% of 200 mg Celecoxib patients). The median time to rescue medication was 3:05 for Celecoxib 200mg; 1:48 for Celecoxib 50mg; 1:32 for Celecoxib 25mg; and 1:17 for placebo. ***[Study 025 Appendix 2.3]***

Duration of analgesic efficacy - LOCF was determined as the time for which a treatment group maintained a statistically significant difference from placebo. Ibuprofen 400mg SD resulted in statistically significant differences from placebo beginning 45 minutes postdose and continuing through Hour 24. Ibuprofen was also superior to 200mg Celecoxib beginning at 45 minutes postdose and continuing for 3 to 5 hours. It was superior to both 25mg and 50mg dosages from 45 minutes through Hour 24.

Peak analgesic effect - LOCF for Ibuprofen 400mg SD in PID score was 1.12 units, whereas Celecoxib 200mg peaked with a score of 0.58 and the 50mg dose with a score of 0.48. The peak scores in Pain Relief (PR) for these 3 treatment groups was 2.28 for Ibuprofen; 1.74 for Celecoxib 200mg; and 1.18 for Celecoxib 50mg. All groups achieved these maximum levels at Hour 3 postdose. The time to onset of perceptible pain relief was 33 minutes for Ibuprofen; 38 minutes for Celecoxib 200mg; and 1 hour 5 minutes for Celecoxib 50mg.

VI. Pain Study 027 - Postsurgical Dental Pain *[Attachment # 5 - Page 31]*

1. Study Design: Study 49-96-02-027 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 and 200 mg SD) with Placebo and Anaprox 550mg SD in patients with moderate to severe postsurgical dental pain following extraction of 2 or more impacted third molar teeth. This study followed the same design and included the same patient population as that of Study N49-96-02-005, however, the study was double-blind and of 24-hour duration. Scheduled pain assessments were made at 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. Additionally, patients were provided two stopwatches with which to record Time to Perceptible and Time to Meaningful Pain Relief.

The study was conducted between 03/04/97 and 07/25/97. The protocol date is 01/28/97. Amendment #1, dated 01/29/97, added the 200mg dose and increased the planned study size to 220. Amendment #2, dated 02/10/97, extended the posttreatment period to 24 hours. Administrative change dated 09/24/97 (2 months following end-of-study) modified the analysis plan based on communications with the FDA. The modifications (1) changed the extrapolation method for missing values to the LOCF method; (2) changed the time windows used in linear interpolation of missing values; (3) added exploratory analysis of time to onset of analgesia; and (4) clarified the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor found treatment groups comparable for age, race, gender, as well as height, weight, and vital signs at Baseline. Of the 220 patients enrolled, none required rescue medication throughout the first hour postdose (ITT cohort period), and 81 completed the Hour 24 assessment without rescue.

The age range of patients in all treatment groups was with the majority less than 30 years old. Across treatment groups, 45% of the patients were male and 36% were Caucasian. The degree of impaction and baseline pain intensity were comparable ($p \geq 0.322$) across all treatment groups. All treatment groups were comparable with respect to number of molars extracted ($p \geq 0.718$, categorical). All treatment groups were comparable with respect to time from surgery until taking study medication and baseline pain intensity on the VAS ($p \geq 0.061$). Mean pain intensity across treatment groups was and mean time until taking study medication was after surgery.

3. Sponsor's Evaluation: The sponsor reports, "Single oral doses of SC-58635 100 mg and 200 mg were safe and well tolerated; and Single oral doses of SC-58635 100 mg and 200 mg provided greater analgesic relief than placebo". *[Study Report 027- Page 103]*

4. Reviewer's Evaluation: *[Attachment # 9 A-B - Pages 37-38]* Both 100mg and 200mg SD Celecoxib showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF, statistically superior mean Pain Relief (PR) began Hour 1 postdose ($p=0.0001$ for 200mg and $p=0.0034$ for 100mg) and continued through Hour 24 ($p=.0001$ for 200mg and $p=0.0206$ for 100mg). Adjusting for multiplicity of multiple comparisons reduces the time length for significance of Celecoxib 100mg to Hour 8 ($p=0.0115$). The mean Pain Intensity Difference (PID) also began 45 minutes postdose and continued through Hour 24. The NSAID agent, Anaprox 550mg, used as a positive control, was not only superior to placebo, but also to the 100mg and 200mg dosage levels of Celecoxib at varying assessment time points. As was seen in the review of Study 025, the results for LOCF offer Celecoxib a slightly better advantage over those for BOCF primarily in that the duration of

statistical significance is longer for LOCF than BOCF. ***[Missing Values - Page 3]***

Mean Pain Intensity Difference (PID-LOCF) ***[Study Report Table 027-9 - Pages 39-41]*** or change from baseline for patients in the 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 45 minutes postdose and continuing through Hour 24. At 30 minutes, Anaprox 550 was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to Celecoxib and placebo through Hour 4, and continued to be statistically superior to placebo and Celecoxib 100mg, and numerically superior to Celecoxib 200mg throughout subsequent assessments.

Mean Pain Relief (PR-LOCF) ***[Study Report Table 027-10 - Pages 43-45]*** for patients in all 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 45 minutes postdose and continuing through Hour 24. At 30 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to Celecoxib and placebo through Hour 5, and continued to be statistically superior to placebo and Celecoxib 100mg, and numerically superior to Celecoxib 200mg throughout the subsequent hourly assessments.

A higher percentage of Anaprox patients achieved a perceptible level of pain relief (93% of Anaprox 550mg patients compared to 51% of placebo; 69% of 100mg; and 79% of 200 mg Celecoxib patients). ***[Study 027 Appendix 2.3]***

Mean Sum of Pain Intensity Difference and Pain Relief (PRID-LOCF) ***[Study Report Table 027-11 - Pages 47-49]*** in the 2 Celecoxib dosage groups (100 and 200 mg SD) showed a statistically significant difference from placebo beginning 30 minutes postdose and continuing through Hour 24. At 30 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. It remained statistically superior to Celecoxib 100mg and placebo through Hour 5, and continued to be statistically superior to Celecoxib 100mg and placebo, and numerically superior to Celecoxib 200mg throughout subsequent assessments.

Median Time to Onset of Perceptible Pain Relief - LOCF ***[Study Report Table 027-12 - Pages 51-52]*** for patients in the Celecoxib 200mg dosage group showed a statistically significant difference from placebo. The positive control, Anaprox 550mg SD, was statistically superior to both the Celecoxib 100 and 200mg levels, as well as placebo. The median time to onset was 0:24 for Anaprox; 0:30 for Celecoxib 200mg; 0:45 for Celecoxib 100mg; and 0:58 for placebo.

Median Time to Administration of Rescue Medication - LOCF ***[Study Report - Page 53]*** revealed that fewer patients in the Anaprox 550mg group required rescue medication than in any other treatment group, followed by those in the Celecoxib 200mg group (46% of Anaprox 550mg compared to 84% of placebo; 69% of 100mg; and 52% of 200 mg Celecoxib patients). The median time to rescue medication was 10:02 for Celecoxib 200mg; 4:17 for Celecoxib 100mg; and 1:20 for placebo.

Duration of analgesic efficacy - LOCF was determined as the time for which a treatment group maintained a statistically significant difference from placebo. Anaprox 550mg SD resulted in statistically significant differences from placebo beginning 30 minutes postdose and continuing through Hour 24. Anaprox was also superior to 100mg and 200mg Celecoxib beginning at 30 minutes postdose and continuing for 4 to 5 hours. It continued to demonstrate a statistically significant difference with Celecoxib 100mg from 30 minutes through Hour 24.

Peak analgesic effect - LOCF for Anaprox 550mg SD in PID score was 1.28 units, whereas Celecoxib 200mg peaked with a score of 0.82 and the 100mg of 0.58. The peak scores in Pain Relief (PR) for these 3 treatment groups was 2.72 for Anaprox; 2.07 for Celecoxib 200mg; and 1.62 for Celecoxib 100mg. All groups achieved these maximum levels at Hours 2 to 3 postdose.

VII. Pain Study 028 - Postsurgical Orthopedic Pain *[Attachment # 6A-B-C - Pages 32-34]*

1. Study Design: Study 49-96-02-028 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 mg and 200 mg BID PRN) with Placebo and Propoxyphene napsylate naprox 100 mg with acetominophen 650 mg (Darvocet-N50 2X) QID PRN in patients with moderate to severe postsurgical orthopedic pain (baseline pain intensity on categorical scale). The orthopedic procedure required open manipulation of bone with periosteal elevation that was expected to require administration of analgesics for management of pain for 3-5 days. Patients were to have received administration of the first dose of study medication within 54 hours after the end of anesthesia.

The study was conducted between 5/6/97 and 3/10/98 by 12 investigators, 11 of whom enrolled at least one patient. The protocol was dated 2/7/97.

Amendment #1 dated 3/4/97, added the treatment group SC-58635 100 mg BID PRN, increased the sample size to 240 patients, added clarification to the evaluation of 3 efficacy measures, "SPID, TOTPAR and SPRID, will be weighted by time intervals between successive evaluations" and changed measurement of vital signs from sitting or supine to supine position only.

Amendment # 2, dated 5/12/97, added clinical laboratory tests, including bleeding time and urine collection, for one study site (SCIREX), and allowed for the collection of screening laboratory test data at all sites.

Administrative Change # 1, dated 6/16/97, removed 12 hour urine collection section on CRFs and added sodium, potassium, chloride, osmolality and creatinine clearance to the normal laboratory values form.

Amendment # 3, dated 7/22/97, increased the time frame from end of anesthesia to first dose of study medication from 48 to 54 hours; added shoulder reconstruction and laminectomy to inclusion criterion #4; added an exclusion criterion #11, which modified the wording of existing exclusion criterion #8, regarding lactose-intolerant patients; and changed the Medical Monitor.

Amendment # 4, dated 11/3/97, allowed patients to continue in the study as outpatients for up to five days; changed the minimum hospital stay after study drug dosing from 24 hours to 12 hours; redefined criteria for "completed patient"; changed exclusion criterion from "has been treated" to "had treatment initiated" for esophageal, gastric, pyloric channel, or duodenal ulceration within 30 days prior to receiving the first dose of study medication; changed exclusion criterion from is willing to abstain from alcohol 24 hours "prior to" surgery to "from" surgery; added exclusion criterion "the patient has cancer and has been in remission, and off any treatment for less than 2 years prior to study enrollment"; added CRFs to capture additional pain assessments at the time of rescue or remedication; and modified the analysis plan based on communications with the FDA, i.e. changed the extrapolation method for missing values to LOCF and changed the time windows used in linear interpolation of missing values.

Administrative Change # 2, dated 12/22/97 (8 months into study and 3 months before end-of-study), changed the Clinical Monitor, outlined the objective of the interim analysis conducted December, 1997 and defined the study's stopping rule. The objectives were to: (1) evaluate the feasibility of the pain model for the study; (2) evaluate the analgesic effect of SC-58635; (3) drop the low dose of SC-58635 100 mg if not efficacious; and (4) re-estimate the variation of the primary efficacy variables for future study design. The active control will be compared to placebo for validation of the pain model. Each of the SC- 58635 100 mg and 200 mg dose groups will be compared to placebo to evaluate the analgesic effect of the study drug. The standard deviation of the primary efficacy variables will be calculated. The study may be stopped for any one the following reasons: (1) Lack of efficacy of SC-58635. An alpha-spending function corresponding to a linear low boundary will be applied for accepting H_0. A significance level of 0.32 (z-value=1.004, two-sided) will be used for accepting H_0.

Patients were allowed to receive analgesic medications such as Patient Controlled Analgesia (PCA) in the postsurgical period prior to first dose of study medication. If they were administered PCA during the postsurgical period, they must have tolerated and received pain relief from an oral analgesic medication prior to receiving study medication.

The Pretreatment Period included the Screening Visit, Surgery, and Baseline. Screening occurred up to 14 days prior to surgery. The Baseline assessment was within 54 hours after the end of anesthesia. The clinical laboratory tests at Screening were repeated. Immediately prior to study drug administration, each patient was asked to record the severity of his or her starting pain and only patients indicating moderate or severe pain were enrolled in the study.

The Treatment Period was defined as up to a 5-day period after the first dose of study medication. Day 1 was defined as the 24-hour period beginning with the date and time of the first dose of study medication. Patients received the second dose not less than four hours after the first dose. Subsequent doses of study medication were administered as needed, no closer than 2 hours apart, and could not exceed 4 doses in 24 hours. In the Celecoxib groups, only the first 2 doses were active; doses 3 and 4 were matching placebo. All 4 doses of Darvocet-N50 (2 tablets) were active. Patients received study medication for up to 5 days maximum.

Patients underwent the following assessments at 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, and 24 hours post-dose: Pain Intensity (Categorical Scale); Pain Relief; Pain at Least Half Gone; and Pain Intensity (VAS). They were also provided with a stopwatch to record Meaningful Pain Relief. Additionally, the APS Pain Measure was completed by each patient every 24 hours after the first dose of study medication. Final pain assessments were performed at the last hourly observation; just prior to rescue analgesia or just prior to hospital discharge.

2. Patient Disposition: Using ANOVA and Pearson's Chi-square testing, the sponsor reports that the treatment groups were comparable for age, race, gender, and with respect to height, weight, and vital signs at Baseline. Of the 255 patients enrolled in 11 centers, only 3 completed the study as per definition in the protocol, i.e. remained in study for 5 full days. Since many of the patients were discharged from the hospital prior to the 5 days, they were ruled noncompliant premature terminations. Because 9 patients [13-0185; 4-0225; 9-0490; and 9-0605 (took rescue medication before the 1-hour pain assessment); 2-0011 and 2-0315 (2 consecutive pain assessments interpolated by the same 2 values within the first 2 hours); 5-0039 (withdrew at Time 0 [spit out study medication]); 9-0135 (predose pain assessments only), and 9-0167 (did not have any pain assessments) were excluded from the ITT cohort for Day 1, the efficacy analysis was based on the remaining sample size of 246.

The age range of patients in all treatment groups was years, with the majority less than 30 years old. Across treatment groups, of the patients were male and were Caucasian. The type of surgical procedure performed and baseline pain intensity were comparable ($p \geq 0.548$ and $p \geq 0.297$ respectively); and duration of surgery, time from end of anesthesia until taking study medication and Baseline Pain Intensity (Visual Analog Scale) were also comparable across all treatment groups ($p \geq 0.279$). Mean duration of surgery across treatment groups was). Mean time from end of anesthesia until taking study medication was . Mean Baseline Pain Intensity (VAS) across treatment groups was

3. Sponsor's Evaluation: The sponsor reports issuing a protocol amendment and interim analysis plan before the interim data set closed, but the analysis, dated December, 1997, appears to have been performed without an *a priori* plan. This was labeled as an administrative change dated 12/22/97, 8 months into study and 3 months before end-of-study. This also changed the Clinical Monitor; outlined the rationale and objective of the interim analysis; and defined the study's stopping rule. The sponsor also reports that an independent Data Monitoring Committee conducted the interim efficacy analysis and made the recommendation to continue the trial as planned. The results of the interim analysis were not disseminated to non-committee members and the study blind was maintained for non-committee members.

The sponsor reports, "In Study 028, the sensitivity of the model to detect statistically significant differences from placebo was limited by the unexpectedly large placebo response at the early assessment times. Nevertheless, the proportion of patients not requiring rescue medication or remedication during the eight hours after dosing was only 2% with placebo contrasted to 10% and 22% ($p < 0.05$) with the 100 mg and 200 mg doses, respectively. The PPID (categorical) scores with Celecoxib 100 mg and 200 mg were similar to values observed in the post-oral surgery studies. However, the lack of statistical significance compared to placebo in Study 028 was due to the larger than expected placebo response in that study."

"Over a 24 hour period patients randomized to Celecoxib received the compound BID PRN, with a minimum dosing interval of 4 hours. Patients randomized to Darvocet-N50 (2 tablets) received medication QID PRN with a minimum dosing interval of 4 hours. The median time to rescue medication or remedication was 04:01 hours for the Celecoxib 100mg BID PRN treatment group and 03:52 hours for the Celecoxib 200mg BID PRN treatment group. These results are similar to the median time to rescue medication (03:48 hours for Celecoxib 100mg SD and 06:03 hours for 200mg SD) derived from the pooled analysis of the post-oral surgery studies. Additional evidence of the analgesic efficacy of this regimen was provided by the proportion of patients remaining in the study at 24 hours after the first dose. At 24 hours after the first dose of study medication the proportion of patients remaining in the study in the Celecoxib 100mg BID PRN treatment group (16/67 or 24%) and the Celecoxib 200mg BID PRN (11/58 or19%) treatment group was similar to the Darvocet-N50 (2X) QID PRN group (17/62 or 27%). All 3 groups had more patients remaining at 24 hours than in the placebo QID PRN group (4/59 or 7%)". *[ISE]*

4. Reviewer's Evaluation: As used in this postsurgical orthopedic pain study, the assessment of analgesic efficacy of the 100mg and 200mg Celecoxib BID PRN doses did not demonstrate a particulary convincing performance as compared to placebo, although the pain assessment scores were numerically greater than those of placebo. For both the single dose and multiple dose analyses of mean Pain Intensity Difference (PID) using BOCF, Celecoxib 200mg BID PRN only showed statistically significant analgesic efficacy compared to placebo during the Hour 6 and Hour 7 assessment periods, however, Celecoxib 100mg and 200mg were

numerically superior to placebo beginning 45 minutes postdose and continuing through Hour 24. For the BOCF (single dose and multiple dose) and LOCF (single dose and multiple dose) analyses, the Celecoxib 100mg BID PRN and 200mg BID PRN doses yielded numerically greater mean PR scores, as well as sporadic statistically significant differences, over placebo. Darvocet N50 (2 tablets) QID PRN used as a positive control, was not only statistically superior to placebo, but also to the 100mg and 200mg dosage levels of Celecoxib at varying assessment timepoints.

Mean Pain Intensity Difference (PID) ***[Study Report Table 028-9-12 - Pages 50-61]*** or change from baseline for patients in all 2 Celecoxib dosage groups (100 and 200 mg BID PRN) showed a statistically significant difference from placebo only during Hours 6 through 7 using single dose analyses for BOCF, and Hours 6 through 8 for LOCF, with statistical significance extending into Hours 10 through 12 using multiple dose analyses. With few exceptions, the mean scores for Celecoxib 200mg were greater than those of Celecoxib 100mg. Darvocet N50 (2X) QID PRN was statistically superior to Celecoxib 200mg between Hours 2 and 4 for BOCF (single dose analyses) and at varying timepoints from Hours 2 through 11 for BOCF (multiple dose analyses). Darvocet was also statistically superior to Celecoxib 100mg between Hours 1 through 5 for BOCF (single dose analyses) and between Hours 1 and 18 for BOCF (multiple dose analyses).

There were statistically significant effects for center and surgery type as well as a treatment by center interaction at various timepoints. Further subgroup analyses were performed for the time-specific primary efficacy measures by center and surgery type. These analyses did not reveal any consistent pattern across timepoints.

Mean Pain Relief (PR) ***[Study Report Table 028-13-16 - Pages 64-75]*** scores (extrapolated for baseline values factored into the analyses) for BOCF showed a statistically significant difference between Celecoxib 100mg and placebo only at Hours 4 or 5 for single and multiple dose analyses; Celecoxib 200mg was statistically superior to placebo only at Hours 6 or 9 for single and multiple dose analyses. The 100mg and 200mg Celecoxib doses were numerically greater than placebo beginning 45 minutes postdose and continuing through Hour 24. Relatively similar results were seen for the LOCF.

Mean PR scores for Darvocet-N50 (2X) QID PRN were statistically superior to placebo at Hours 2 through 6 for BOCF single dose analysis; at Hours 2 through 18 for BOCF multiple dose analysis; at Hours 2 through 7 and 24 for LOCF single dose analysis; and at Hours 1.5 through 24 for LOCF multiple dose analysis ($p=0.0105$ at Hour 1.5 and $p=0.0068$ at Hour 24). For the BOCF single dose analysis, the mean PR scores for Darvocet-N50 were statistically superior to Celecoxib 200mg BID PRN at Hour 5, and Celecoxib 100mg BID PRN at Hours 2 and 5. For the BOCF multiple dose analysis, Darvocet-N50 (2 tablets) QID PRN demonstrated a statistically significant difference from Celecoxib 200mg at Hours 5, 10, 11, and 18; and from Celecoxib 100mg at Hours 2, 3, and 6 through Hours 11 and 18. For LOCF, the mean PR scores for Darvocet-N50 (2X) QID PRN were statistically superior to Celecoxib 100mg at Hours 6 and 18.

VIII. Pain Study 029 - Postsurgical General Nonorthopedic Pain *[Attachment # 7 - Pg 35]*

1. Study Design: Study 49-96-02-029 was a double-blind, placebo-controlled comparison of safety and efficacy of 2 doses of Celecoxib (100 and 200 mg) BID PRN with Placebo and Propoxyphene napsylate 100 mg with acetominophen 650 mg (Darvocet-N50) QID PRN in patients with moderate to severe post-general (non-orthopedic) surgical pain (baseline pain intensity on categorical scale). The general surgical procedure was expected to require

administration of analgesics for management of pain for 3 - 5 days. This study followed the same design as that of Post-surgical Orthopedic Pain Study N49-96-02-028.

The study was conducted between 05/12/97 and 01/18/98 by 13 U.S. and 1 New Zealand investigator, 12 of whom enrolled at least one patient. The protocol date is 02/07/97.

Amendment #1, dated 03/04/97 before start-of-study, added the treatment group SC-58635 100 mg PRN up to BID; increased the sample size to 240; added clarification to the evaluation of efficacy; and changed the measurement of vital signs from sitting or supine to supine only.

Amendment #2, dated 05/09/97, added clinical laboratory tests, bleeding time, and urine collection for 1 study site (SCIREX) and allowed for the collection of screening laboratory test data at all sites.

Administrative change dated 06/16/97 (1 month into study) removed the 12-Hour Urine Collection section on 3 CRFs; added sodium, potassium, chloride, osmolality, and creatinine clearance to the Normal Lab Values Form; and corrected the spelling of the laboratory name.

Amendment #3, dated 07/22/97 (2 months into study) increased the time frame from end of anesthesia to first dose of study medication from 48 to 54 hours; added an exclusion criterion #12 which modified the wording of the exclusion criteria regarding lactose intolerant patients; and changed the Medical Monitor.

Amendment #4, dated 11/03/97 (1 month before end-of-study), allowed patients to continue in the study as outpatients for up to five days; changed the minimum hospital stay after study drug dosing from 24 hours to 12 hours; redefined the criteria for a "completed patient"; modified exclusion criteria #2, #4, #5 and #8; captured additional pain assessments on the CRFs at time of rescue or remedication; and modified the analysis plan for the study based on communications with the FDA. The modifications consisted of: changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; and changing the time windows used in lineal interpolation of missing values.

Administrative change #2, dated 12/22/97 (1 month before end-of-study), outlined the rationale and objective of the interim analysis conducted in December 1997; defined the study's stopping rule; and changed the Clinical Monitor and the Statistician.

2. **Patient Disposition:** Across all groups, there were 19 patients who violated one or more entry criteria. These included 6 patients in the placebo group, 4 patients in the SC-58635 100 mg BID PRN group, 6 patients in the SC-58635 200 mg BID PRN group, and 3 patients in the Darvocet-N 100mg QID PRN group.

A total of 167 patients were enrolled in this study before the study was discontinued. All randomized patients received at least one dose of study medication. Of the 167, only 2 (1%) completed the study as per definition in the protocol, i.e. remained in study for 5 full days. The remaining 165 (99%) withdrew prior to completing the full five days of the study. Since many of the patients were discharged from the hospital prior to completion of the 5 days, they were ruled noncompliant premature terminations.

3. **Sponsor's Evaluation:** Out of the 167 patients, 7 were excluded from the efficacy analysis. Six of these (patients NZ0007-0448, US0004-0404 and US0011-0474 in the Darvocet-N 100 mg

QID PRN treatment group; patients US0008-0478 and US0009-0129 in the SC-58635 200 mg BID PRN treatment group; and patient US0011-0527 in the SC-58635 100 mg BID PRN treatment group) terminated from the study prior to the one hour assessment.

4. Reviewer's Evaluation: This review did not perform an efficacy analysis on this study, which was discontinued prior to full enrollment. Across all groups, there were 19 patients who violated one or more entry criteria. Of the 167 patients enrolled, only 2 (1%) completed the study as per definition in the protocol, i.e. remained in study for 5 full days. The remaining 165 (99%) withdrew prior to completing the full five days of the study.

IX. Pain Study 070 - Postsurgical Dental Pain *[Attachment # 8 - Page 36]*

1. Study Design: Study 49-96-02-070 was a double-blind, placebo-controlled comparison of safety and efficacy of 4 doses of Celecoxib (50, 100, 200, and 400 mg) with Placebo and Anaprox 550 mg in patients with moderate to severe postsurgical dental pain following extraction of 1 or more impacted third molar teeth involving mandibular bone removal.

The study was conducted between 4/17/97 and 7/1/97.. The protocol was dated 12/30/97. Administrative Change # 1, dated 9/24/97 (3 months after end-of-study), modified the analysis plan based on communications with the FDA. The modifications consisted of: (1) changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; (2) changing the time windows used in linear interpolation of missing values; (3) adding exploratory analysis of time to onset of analgesia; and (4) clarifying the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

2. Patient Disposition: Forty nine (49) patients completed the 24-hour assessment period without taking rescue medication and completed the scheduled 24.0 hour assessments. Two hundred and six (206) patients took rescue medication during the 24 hour assessment period. One Celecoxib 50 mg patient (#539), who took rescue medication, withdrew from the study due to an adverse event (alveolar osteitis on Day 21 post-treatment).

The treatment groups were comparable for age, race, and gender. For all treatment groups, the age range was years (majority less than 30 years old). Across treatment groups of the patients were female and , were Caucasian ($p \geq 0.960$). All treatment groups were comparable ($p \geq 0.318$) with respect to height, weight, and vital signs at Baseline.

The treatment groups were comparable ($p \geq 0.072$) for surgical trauma rating, degree of impaction, and number of molars extracted. There was a slightly greater percentage of Placebo, Celecoxib 100mg and 200mg patients with severe pain intensity (52%, 58% and 44%, respectively) than in the naproxen sodium 550 mg, Celecoxib 50 mg, and 400 mg treatment groups (29%, 40% and 23%, respectively). Although this difference was statistically significant ($p=0.010$), the sponsor did not consider it clinically relevant for purposes of this study. All treatment groups were comparable with respect to time from surgery until taking study medication ($p \geq 0.115$). The mean time until study medication was The mean Baseline pain intensity across treatment groups was

3. Sponsor's Evaluation: The sponsor reports, " Celecoxib 50 mg was a submaximally efficacious dose as higher doses of Celecoxib were associated with a greater degree of analgesic efficacy ... demonstrated and replicated in Studies 027 and 070. In Study 070, the

responses to these doses provided similar efficacy while in Study 027 the magnitude of the response was greater with 200 mg. As shown in Study 070, a dose of 400 mg offered some improved analgesic efficacy when compared to 100 mg or 200 mg." ***[ISE]***

The sponsor summarized "Results of this study were comparable to those seen in 3 previous postsurgical dental pain studies. In these studies, SC-58635 (100, 200, and 400 mg) provided statistically significant greater analgesic efficacy than placebo during most of the treatment periods. In general, greater efficacy (earlier onset of relief and greater duration of relief) has been observed with increasing doses of SC-58635 with this difference reaching statistical significance at the 8 hour through 24 hour assessment times. It is therefore concluded that in this study: Single oral doses of SC-58635 50 mg, 100 mg, 200 mg, and 400 mg were safe and well tolerated; Single oral doses of SC-58635 50 mg, 100 mg, 200 mg, and 400 mg provided greater analgesic activity than placebo in patients with moderate to severe postsurgical dental pain; and SC-58635 50 mg was a submaximally effective therapeutic dose." ***[Study Report 070 - Page 4]***

4. Reviewer's Evaluation: ***[Attachment # 9 A-B - Pages 37-38]*** The ITT Cohort was the entire patient enrollment of 255 randomized to single doses of Placebo; Naproxen sodium 550 mg; and 3 Celecoxib arms at 50mg, 100mg, 200mg, and 400mg.

With varying onset time and duration of effect, all SD dosage groups of Celecoxib (400mg, 200mg, 100mg, and 50mg) showed statistically significant analgesic efficacy compared to placebo when used in a postsurgical dental pain model. For LOCF in the 400mg, 200mg, and 100mg dosage groups, statistically superior mean Pain Relief (PR) began 1 hour postdose (p=.0210 for 400mg; p=0.0080 for 200mg; and p=0.0036 for 100mg) and continued through Hour 24 (p=.0001 for 400mg; p=0.0026 for 200mg; and p=0.0103 for 100mg). The mean Pain Intensity Difference (PID) began 1 to 1.5 hours postdose and continued through Hour 24. Although the 50mg SD Celecoxib group also demonstrated statistical superiority over placebo, the separation began at a later postdose timepoint (1.5 hours) and only continued through Hour 6 for PID and Hour 8 for PR. However, positive control Anaprox 550mg was superior to placebo beginning 45 minutes postdose through Hour 24, and superior to all 4 dosage levels of Celecoxib beginning 45 minutes postdose through Hours 4 to 6, depending on the dosage level.

Mean Pain Intensity Difference (PID-LOCF) ***[Study Report Table 070-9 Pages 39-41]*** or change from baseline for patients in 3 Celecoxib dosage groups (100, 200, and 400 mg SD) showed a statistically significant difference from placebo beginning 1 hour postdose and continuing through Hour 24. At 45 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to placebo through Hour 24. It was statistically superior to Celecoxib 400mg through Hour 4; to Celecoxib 200 mg through Hour 5; and to Celecoxib 100 mg and 50 mg through Hour 6.

Mean Pain Relief (PR-LOCF) ***[Study Report Table 070-10 - Pages 44-46]*** for patients in 3 Celecoxib dosage groups (100, 200, and 400 mg SD) showed a statistically significant difference from placebo beginning 1 hour postdose and continuing through Hour 24. At 45 minutes, positive control Anaprox 550mg was statistically superior to all levels of Celecoxib, as well as placebo. Anaprox remained statistically superior to placebo through Hour 24. It was statistically superior to Celecoxib 400mg through Hour 3; to Celecoxib 200 and 100 mg through Hour 4; and to Celecoxib 50 mg through Hour 8.

X. Pain Study 080 - Postsurgical Orthopedic Pain

Study 49-96-02-080 was a double-blind, placebo-controlled comparison of safety and efficacy of 1 dose of Celecoxib (200 mg) with Placebo and Naproxen 500 mg in patients with moderate to severe postsurgical orthopedic pain.

The sponsor reports, "Study 080 had only one patient enrolled when a decision was made to discontinue the study because the comparator selected was not considered to be suitable for the pain model. Because there was only one patient enrolled and that patient had been randomized to the active control, the results from Study 080 are not included in the discussions of the efficacy results for the mangement of pain". ***[Index ISE Page 236 of 1256]***

XI. Overall Review Conclusions *[Attachments # 9 - 13 - Pages 37 - 46]*

The sponsor conducted 7 studies to investigate the analgesic efficacy of Celecoxib as an agent for acute pain. Results and data from 5 of these were reviewed under this submission. The seventh study (080) was terminated after enrolling 1 patient in the positive control arm, which was deemed an inappropriate control agent for a postsurgical orthopedic pain model. Another study (029) using a postsurgical general nonorthopedic model, was terminated after the sponsor's interim analysis. Of the 5 studies reviewed, 4 used postsurgical dental pain models (005; 025; 027; 070); and one used a postsurgical orthopedic model (028).

With regard to postsurgical dental pain, this review is in agreement with the sponsor's conclusions regarding the management of pain ***associated with postoperative dental procedures***. "In summary, studies conducted in multiple clinical settings support the analgesic efficacy of the following dosing regimen in the management of pain: Celecoxib 100 mg or 200 mg as needed every 4-6 hours, up to a maximum total daily dose of 400 mg. Some patients may derive additional efficacy from an initial dose of 200 mg. The active controls were included in the postsurgical pain studies to validate the sensitivity of the model in assessing analgesic efficacy. In general, in the single dose post-oral surgery studies, the NSAID comparators demonstrated a more rapid onset of analgesia and a greater peak response than Celecoxib at the doses studied (25 mg SD, 50 mg SD, 100 mg SD, 200 mg SD, 400 mg SD." ***[ISE]***

1. Efficacy: *[Attachments # 9 - 13 A-B - Pages 37 - 46]*

Postsurgical Dental Pain: The evaluation of Celecoxib's analgesic efficacy is based on only 1 acute pain model, that of postsurgical dental pain or third molar extraction during oral surgery. Celecoxib 100 mg was found to be statistically superior to placebo in 3 of these dental pain studies (005; 027; 070). The 200 mg dose was also found to be statistically superior to placebo in 3 dental pain studies (025; 027; 070). And the 400 mg dose was found to be statistically superior to placebo in 2 postsurgical dental pain studies (005; 070) although Study 005 was a Phase 2, single-blind study and may not constitute an adequate and well-controlled trial. The 25 mg and 50 mg doses used in postsurgical dental pain studies did not show sufficiently efficacious analgesic effect, most especially with respect to duration of effect. Statistically significant differences in primary efficacy measures for the Celecoxib dose groups from those of the placebo groups are seen in graphical representation for Mean Pain Relief and Mean Pain Intensity Difference presented in ***Attachments***

10A (LOCF) and 10B (BOCF) on Pages 39 - 40, and Attachments 12A (LOCF) and 12B (BOCF) on Pages 43 - 44.

The robustness of study results is evidenced by the graphical summary of mean Pain Relief for each Celecoxib dose level (placebo included as a reference measure) in ***Attachments 11A (LOCF) and 11B (BOCF) on Pages 41 - 42.***

Onset: The post dose time at which Celecoxib demonstrated statistically significant differences from placebo with regard to pain relief (PR) and pain intensity difference (PID) was 45 minutes to 1 hour. The positive control Ibuprofen 400mg demonstrated a comparable onset in Study 025, whereas Naproxen 550 mg in Study 027 separated from placebo earlier, beginning 30 minutes postdose. In Study 070 the time for both positive control and Celecoxib was later perhaps due to the particular patient sample of this study. Naproxen demonstrated statistically significant differences from placebo at 45 minutes, and Celecoxib at 1 hour postdose. Patients in both the NSAID and Celecoxib 100 mg, 200 mg, and 400 mg dose groups maintained a statistically significant separation from placebo throughout the remaining assessments, including the final Hour 24 time point. This time to onset of statistically significant differences is tabulated and graphically presented in ***Attachments # 13 A-B - Pages 45 - 46.***

The significant p-values (both adjusted and nonadjusted for the multiplicity of multiple comparisons) of pairwise Treatment Mean comparisons are tabulated in ***Attachments 9A (LOCF) and 9B (BOCF) - Pages 37 - 38.*** The more conservative BOCF method yielded shorter durations for which statistical separation from placebo can be maintained. However, as was described by the sponsor, "with the BOCF method, the estimated missing pain assessments, using the patient's baseline pain intensity, may reflect the patient's status hours before termination from the study. This method does not account for partial improvement at the time of discontinuation. It could potentially create a bias against the treatment group in which patients discontinue with improvement from baseline, however, it is included to provide an additional frequently used method of imputing missing data. On the other hand, the LOCF method, which estimates the missing value by using the observation obtained at the nearest time point, may better reflect reality and patient experiences. It has the closest temporal relation to the patient's status at the time of discontinuation".

The actual efficacy parameter, "time to onset of perceptible pain relief" yielded more favorable results. The median time to onset of perceptible pain relief was slightly shorter than that of demonstrating statistical significance with regard to PR and PID. Ibuprofen 400 mg had a median onset time of 33 minutes, and Naproxen 550mg had onsets of 24 minutes in Study 027 and 36 minutes in Study 070. Celecoxib 400 mg patients had median onset time of 43 minutes; Celecoxib 200 mg patients had median onset times of 38 minutes (Study 025), 30 minutes (Study 027), and 44 minutes (Study 070). Celecoxib 100 mg patients had median onset times of 45 minutes (Study 027) and 39 minutes (Study 070).

Peak: The examination of peak pain relief found that patients in the positive control NSAID groups attained a greater level of pain relief at an earlier post dose time than did those in the Celecoxib and placebo groups. ***[Attachment # 13 A - Page 45]***

Naproxen 550mg patients realized a mean peak pain relief of 2.72 units at Hour 2 (Study 027) and 2.5 at Hour 3 (Study 070). These peak scores translate between the pain relief scores of

"some" and "lot" with scores of 0=none; 1=little; 2=some; 3=lot; 4=complete. However, at best, Celecoxib provided no more than "some" pain relief at its peak. The Celecoxib mean scores for peak pain relief occurred at later postdose times and at lower levels: Celecoxib 400 mg peaked at 1.94 PR units at Hour 4 (Study 070). Celecoxib 200 mg peaked at 2.05 PR units at Hour 4 (Study 027); at 1.74 PR units at Hour 2 (Study 025); and at 1.64 PR units at Hour 2 (Study 070). Celecoxib 100 mg peaked at 1.62 PR units at Hour 4 (Study 027) and at 1.64 PR units at Hour 3 (Study 070). The 50 mg and 25 mg Celecoxib groups peaked at even lower levels: Celecoxib 50 mg peaked at 1.22 PR units at Hour 4 (Study 025) and Celecoxib 25 mg peaked at 1.11 PR units at Hour 1.5 (Study 025). Peak pain relief for placebo patients was at Hour 24.

Duration: The length of time for which each treatment group maintained a statistically significant separation from Placebo with regard to Pain Relief (using BOCF) was greatest for patients in the Naproxen treatment groups, followed by those in the 200 mg and 400 mg Celecoxib groups. Patients in Celecoxib 200 mg and 400 mg dose groups maintained a statistically significant separation from placebo beginning 45 minutes (Study 027) to 1 hour (Study 070) and continued throughout the remaining assessments, including the final Hour 24 time point. The 100 mg Celecoxib group began at Hour 1 post dose but only continued to separate statistically from placebo through Hour 6 (Study 027) and Hour 12 (Study 070). Naproxen demonstrated statistically significant differences from placebo at 30 minutes (Study 027) and 45 minutes (Study 070) post dose and continued through Hour 24. Ibuprofen 400mg demonstrated statistically significant differences beginning 30 minutes into Study 025 and only continuing through Hour 8. ***[Attachments 9A (LOCF) and 9B (BOCF) - Pages 37 - 38; tabulated in Attachment 13A (BOCF) - Page 45; and graphically shown by Attachment 13B - Page 46].***

Evaluating duration by the median time to Rescue Medication found slightly shorter times than that of demonstrating statistical significance with regard to Pain Relief. Ibuprofen 400 mg had a median rescue time of 7 hours, and Naproxen 550mg had rescue times of > 24 hours in Study 027 and 7 hours in Study 070. Celecoxib 400 mg patients had median time to rescue of 8 hours and 13 minutes; Celecoxib 200 mg patients had median rescue times of 3 hours and 5 minutes (Study 025), 10 hours and 2 minutes (Study 027), and 4 hours and 15 minutes (Study 070). Celecoxib 100 mg patients had median rescue times of 4 hours and 17 minutes (Study 027) and 2 hours and 36 minutes minutes (Study 070).

Postsurgical Orthopedic Pain: The results from only 1 postsurgical orthopedic study (Study 028) demonstrate marginal analgesic efficacy that might be considered supportive to a second study using the same model if that study were to show positive results regarding analgesic efficacy for this indication. The sponsor reports that the PPID efficacy responses for the 100 mg and 200 mg arms of Study 028 were comparable to those found in the postsurgical dental pain studies, however, there was no consistent evidence of statistically significant differences as compared to placebo. The sponsor believes this was due to an unusually high placebo response in this study, but did not pursue a second study using this pain model. ***[Attachments # 6 A-B-C - Pages 32 - 34]***

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2. Safety: *[Attachments # 2 A-B-C - Pages 26 - 28]* Safety comparisons of Celecoxib with active comparators should have been made at comparable efficacious doses, i.e. in order to compare safety profiles, the doses of Celecoxib as compared to that of active comparators should be delivering at least the same level of efficacy to the patients in the study. Even though the efficacy levels of Celecoxib are shown to be lower than those of the active control agents, the overall safety profiles appear similar, with the exception of a higher percentage incidence of alveolar osteitis reported by the Celecoxib group.

3. Other Reviewer Comments: In Study 005, Administrative Change #2, dated 10/25/95 (almost 1 month after end-of-study), modified the statistical sections of the protocol. The sponsor reports that this was done to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Studies Using Acute Pain Models", Jan 1995).

In 4 studies, the sponsor changed Clinical Monitors and appears to have performed 2 interim analyses without *a priori* planning as per protocol:

In Study 027, an Administrative change dated 09/24/97 (2 months following end-of-study) modified the analysis plan based on communications with the FDA. The modifications (1) changed the extrapolation method for missing values to the LOCF method; (2) changed the time windows used in linear interpolation of missing values; (3) added exploratory analysis of time to onset of analgesia; and (4) clarified the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

Study 028 had a protocol amendment and detailed interim analysis plan issued before the interim data set closed, but the analysis (dated December, 1997) appears to have been performed without an *a priori* interim analysis plan. This was labeled as an administrative change dated 12/22/97, 8 months into study and 3 months before end-of-study. The Administrative change also changed the Clinical Monitor, outlined the rationale and objective of the interim analysis and defined the study's stopping rule. The sponsor also reports that an independent Data Monitoring Committee conducted the interim efficacy analysis and made the recommendation to continue the trial as planned. The results of the interim analysis were not disseminated to non-committee members and the study blind was maintained for non-committee members. More may be learned by a DSI examination of this study. The stated objectives of the interim analysis were to: (1) evaluate the feasibility of the pain model for the study; (2) evaluate the analgesic effect of SC-58635; and (3) re-estimate the variation of the primary efficacy variables for future study design.

Study 029 also had an administrative change with the very same date of 12/22/97 (1 month before end-of-study), which outlined the rationale and objective of an interim analysis also conducted in December 1997; defined the study's stopping rule; and also changed the Clinical Monitor and the Statistician.

Study 070 also had an Administrative change that was dated the same as that of Study 027, 9/24/97 (3 months after end-of-study). It modified the analysis plan based on

communications with the FDA. The modifications consisted of: (1) changing the extrapolation method for missing values to the last observation carried forward (LOCF) method; (2) changing the time windows used in linear interpolation of missing values; (3) adding exploratory analysis of time to onset of analgesia; and (4) clarifying the name of one of the primary measures of efficacy. The medical monitor for this study was also changed.

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Lillian Patrician, MS, MBA
Mathematical Statistician

cc: Orig. NDA 20-998
HFD-550
HFD-550/Dr. DeLap
HFD-550/Dr. Hyde
HFD-550/Dr. Witter
HFD-550/Dr. Averbuch
HFD-550/Ms. Lutwak
HFD-725/File
HFD-725/Ms. Patrician
Chron.

This review has forty-six [46] pages including thirteen [13] attachments.

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Study Description for Post-Surgical Pain Studies
N49-96-02- 005 / 025 / 027 / 028 / 029 / 070 / 080

Study	Noteworthy Actions	Study Dates	Title of Protocol	Regimen: Enrollment
005	Adm Change #2 of 10/25/95 (1 month after end-of-study), modified stat sections of protocol to reflect the FDA draft guidance ("Presentation of Efficacy Results of Single-Dose Analgesics for Acute Pain Models", Jan 1995) .	8/23/95 to 10/3/95	Single-blind, Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Aspirin 650 mg in Patients with moderate to severe postsurgical dental pain following extraction of third molar teeth.	n=50 Celecoxib 100 mg SD n=50 Celecoxib 400 mg SD n=50 Aspirin 650 mg SD n=50 Placebo
025		7/9/96 to 11/7/96	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 3 Doses of Celecoxib with Placebo and Ibuprofen 400 mg in Patients with moderate to severe postsurgical dental pain following extraction of molar teeth involving mandibular bone removal.	n=50 Celecoxib 25 mg SD n=50 Celecoxib 50 mg SD n=50 Celecoxib 200 mg SD n=50 Ibuprofen 400 mg SD n=50 Placebo
027	Admin change of 09/24/97 (2 months following end-of-study) modified analysis plan based on communications with the FDA and changed the Medical Monitor.	3/4/97 to 7/25/97	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Anaprox 550 mg in Patients with moderate to severe postsurgical dental pain following extraction of 2 or more impacted third molar teeth.	n=55 Celecoxib 100 mg SD n=56 Celecoxib 200 mg SD n=54 Naproxen Na 550 mg SD n=55 Placebo
028	Admin Change # 2 of 12/22/97 (8 months into study and 3 months before end-of-study), changed the Clinical Monitor, outlined the rationale for 12/97 interim analysis, and defined stopping rule.	5/6/97 to 3/10/98	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib with Placebo and Propoxyphene napsylate naprox 100 mg with acetominophen 650 mg (Darvocet-N50) in Patients with mod to severe postsurgical orthopedic pain.	n=68 Celecoxib 100 mg BID PRN n=62 Celecoxib 200 mg BID PRN n=65 Darvocet-N50 (2X) QID PRN n=60 Placebo
029	Admin change of 12/22/97 (1 month before end-of-study), outlined the rationale for 12/97 interim analysis; defined stopping rule; and changed the Clinical Monitor and the Statistician. Study terminated.	5/12/97 to 1/18/98	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 2 Doses of Celecoxib BID PRN with Placebo and Propoxyphene napsylate 100 mg with acetominophen 650 mg (Darvocet-N50) QID PRN in Patients with mod to severe post-general (non-orthopedic) surgical pain.	n=45 Celecoxib 100 mg BID PRN n=42 Celecoxib 200 mg BID PRN n=40 Darvocet-N50-2X QID PRN n=40 Placebo
070	Admin change of 9/24/97 (3 months after end-of-study) changed analysis plan and Medical Monitor.	8/23/95 to 10/3/95	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 4 Doses of Celecoxib with Placebo and Anaprox 550 mg in Patients with moderate to severe postsurgical dental pain following extraction of 1 or more impacted third molar teeth involving mandibular bone removal.	n=35 Celecoxib 50 mg SD n=50 Celecoxib 100 mg SD n=50 Celecoxib 200 mg SD n=35 Celecoxib 400 mg SD n=35 Naproxen Na 550 mg SD n=50 Placebo
080	Study terminated after 1 Naproxen patient enrolled due to inappropriate control for model.	8/23/95 to 10/3/95	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of 1 Dose of Celecoxib with Placebo and Naproxen 500 mg in Patients with moderate to severe postsurgical orthopedic pain.	n=50 Celecoxib 200 mg BID PRN n=51 Naproxen 500 mg BID PRN n=50 Placebo

** Dose Level Summary of Adverse Experiences Reported in All Acute Pain Studies

Reviewer's Results	Placebo	Cele 25 mg	Cele 50 mg	Cele 100 mg	Cele 200 mg	Cele 400 mg	IBU 400 mg	Aspirin 650 mg	Naproxen 550 mg	Darvocet 100 mg	Total
# Enrolled (Safety Evaluable)	305	50	85	268	260	85	50	50	89	105	1347
# Pats with No AE (%)	182 (60%)	27 (54%)	45 (53%)	174 (65%)	143 (55%)	55 (65%)	27 (54%)	33 (66%)	54 (61%)	55 (52%)	795
# Pats with Any AE (%)	123 (40%)	23 (46%)	40 (47%)	94 (35%)	117 (45%)	30 (35%)	23 (46%)	17 (34%)	35 (39%)	50 (48%)	552
# Pats w Trt-rel AE (%) -- Investigator: Uncer/Probable	71 (23%)	05 (10%)	16 (19%)	64 (24%)	71 (27%)	17 (20%)	06 (12%)	12 (24%)	18 (20%)	38 (36%)	318
# Pats w Trt-rel AE (%) -- Sponsor's Medical Opinion	54 (18%)	03 (06%)	11 (13%)	55 (21%)	57 (22%)	12 (14%)	02 (04%)	06 (12%)	13 (15%)	35 (33%)	248
Incidence of Adv Reactions	214	44	58	172	211	46	36	39	68	107	995
Maj Incidence - Nausea	23	07	12	30	34	08	04	11	16	15	160 (12%)
Maj Incidence - Headache	40	07	07	21	22	06	07	03	18	08	139 (10%)
Maj Incidence - Alv Osteitis	18	09	15	10	20	08	06	0	10	0	96 (7%)
Maj Incidence - Vomiting	14	04	03	12	13	04	02	05	06	06	69 (5%)
Maj Incidence - Dizziness	11	03	06	11	14	0	03	05	01	04	58 (4%)

*** Doses were primarily single dose in postsurgical dental pain studies.*
The maximum dosage from remaining postsurgical studies was BID for 5 days duration.

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NDA 20-998 Celebrex (Celecoxib) Attachment # 2 B

Summary of Adverse Experiences Reported in All Acute Pain Studies

Reviewer's Results	Placebo	All Celecoxib Dosage Groups (1- 5 days single dose)	Positive Control Dosage Groups	Total
# Enrolled (Safety Evaluable)	305	748	294	1347
# Completed Study (%)	205 (67%)	531 (71%)	189 (64%)	925 (69%)
# Discontinued Due to AE (%)	08 (03%)	16 (02%)	06 (02%)	30 (02%)
# Disc Due to Trmnt Failure (%)	78 (26%)	147 (20%)	66 (22%)	291 (22%)
# Disc Due to Noncompl (%)	08 (03%)	48 (06%)	32 (11%)	88 (07%)
# Disc Due to Protl Violation (%)	04 (01%)	05 (01%)	0 (0%)	09 (01%)
# Disc by Lost-to-Follow-up (%)	02 (01%)	01 (0%)	01 (0%)	04 (0%)
# Pats with Any AE (%)	123 (40%)	304 (41%)	125 (43%)	552 (41%)
# Pats w Severe AE (%)	29 (09%)	64 (09%)	31 (11%)	124 (09%)
# Adv Reactions (per patient)	214 (0.70)	531 (0.71)	250 (0.85)	995 (0.74)
Incidence of Severe AE (%)	34 (11%)	88 (12%)	41 (14%)	163 (12%)
Major Incidence - Nausea	23 (08%)	91 (12%)	46 (16%)	160 (12%)
Major Incidence - Headache	40 (13%)	63 (08%)	36 (12%)	139 (10%)
Major Incidence - Alv Osteitis	18 (06%)	62 (08%)	16 (05%)	96 (07%)
Major Incidence - Vomiting	14 (05%)	36 (05%)	19 (06%)	69 (05%)
Major Incidence - Dizziness	11 (04%)	34 (05%)	13 (04%)	58 (04%)

Low Incidence Adverse Experiences Reported in All Acute Pain Studies

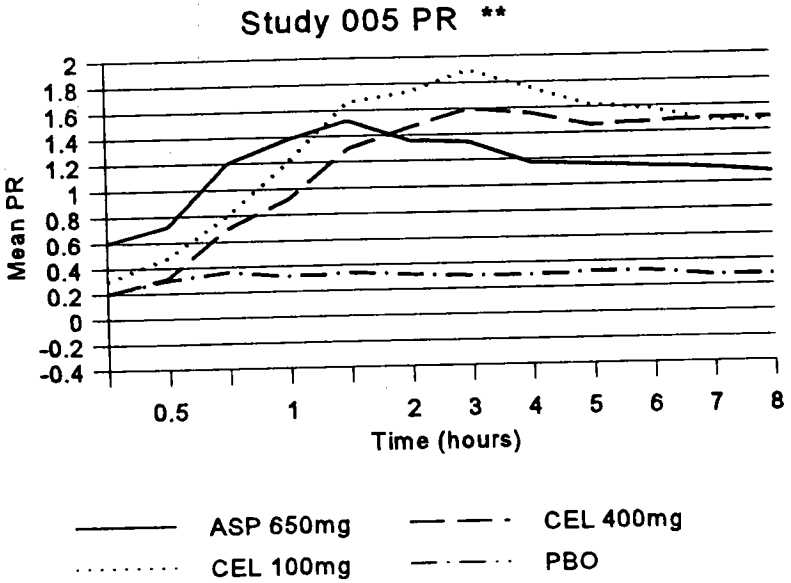
Adverse Experience	Placebo n=305	Celecoxib n=748	Active Controls n=294
Anxiety	0 (0%)	2 (< 1%)	0 (0%
Confusion	1 (< 1%)	5 (1%)	0 (0%)
Diarrhea	2 (< 1%)	7 (1%)	2 (1%)
Dyspepsia	5 (2%)	14 (2%)	4 (> 1%)
Epistaxis	0 (0%)	3 (< 1%)	0 (0%)
Fatigue	0 (0%)	2 (< 1%)	0 (0%)
Glycosuria	0 (0%)	1 (< 1%)	0 (0%)
Gout	0 (0%)	1 (< 1%)	0 (0%)
Hot Flushes	0 (0%)	5 (1%)	2 (1%)
Hyperkalemia	0 (0%)	1 (< 1%)	0 (0%)
Hyperkinesia	0 (0%)	1 (< 1%)	0 (0%)
Hypokinesia	0 (0%)	1 (< 1%)	0 (0%)
Ileus	0 (0%)	1 (< 1%)	0 (0%)
Influenza-like Symptoms	0 (0%)	3 (< 1%)	0 (0%)
Increased LDH	0 (0%)	1 (< 1%)	0 (0%)
Menorrhagia	0 (0%)	1 (< 1%)	0 (0%)
Myalgia	0 (0%)	2 (< 1%)	0 (0%)
Oral Hemorrhage	0 (0%)	6 (1%)	1 (< 1%)
Pallor	0 (0%)	2 (< 1%)	0 (0%)
Pneumothorax	0 (0%)	1 (< 1%)	0 (0%)
Somnolence	5 (2%)	22 (3%)	8 (3%)
Abnormal Stools	0 (0%)	1 (< 1%)	0 (0%)
Stupor	0 (0%)	1 (< 1%)	0 (0%)
Upper Respiratory Tract Infection	1 (< 1%)	6 (1%)	2 (1%)

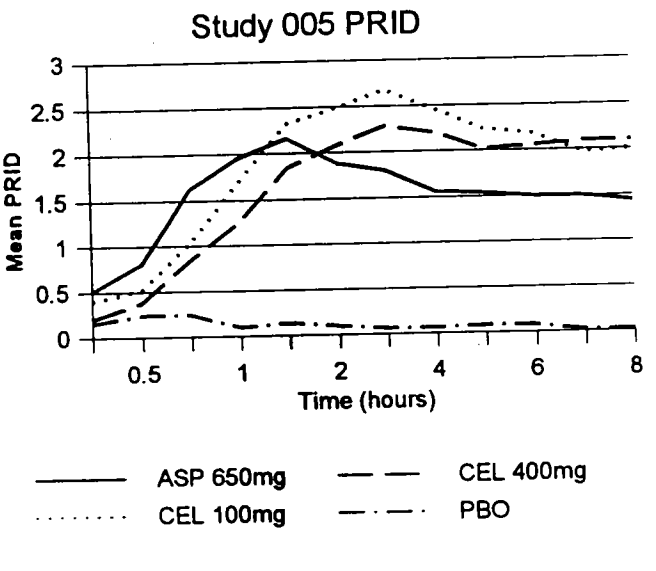
Demographic Summary for PostSurgical Dental Pain Study

Phase 2 Study 49-96-02-005

Reviewer's Results - Study 005	Placebo	Cele 100mg SD	Cele 400mg SD	Aspirin 650mg SD
# Enrolled (Safety Evaluable)	50	50	50	50
# Completed Study (%)	48 (96%)	50 (100%)	49 (98%)	49 (98%)
# Terminations (%)	47 (94%)	30 (60%)	28 (56%)	36 (72%)
- Due to Lost-to-follow-up	2 (04%)	0 (0%)	1 (02%)	1 (02%)
* - Due to Trt Fail/Resc Med	0 (0%)	0 (0%)	0 (0%)	0 (0%)
*- Due to Trt Fail/Resc	45 (90%)	30 (60%)	27 (54%)	35 (70%)
- Due to Adverse Reaction	0 (0%)	0 (0%)	0 (0%)	0 (0%)
# Pats with Any AE (%)	12	13	15	17
# Pats w Trt-rel AE (%)	10	06	12	12
# Males (%)	18 (36%)	22 (44%)	25 (50%)	21 (42%)
# Females (%)	32 (64%)	28 (56%)	25 (50%)	29 (58%)
# Caucasian (%)	35 (70%)	42 (84%)	41 (82%)	39 (78%)
# Hispanic (%)	06 (12%)	05 (10%)	06 (12%)	09 (18%)
# Other (%)	09 (18%)	03 (06%)	03 (06%)	02 (04%)

** *Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*

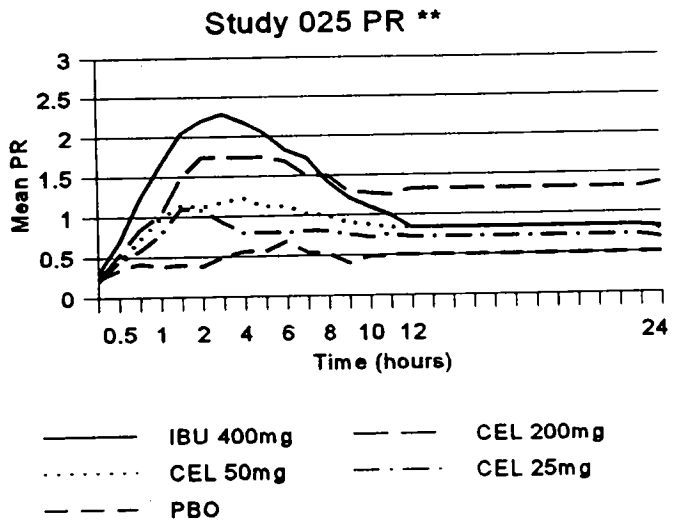


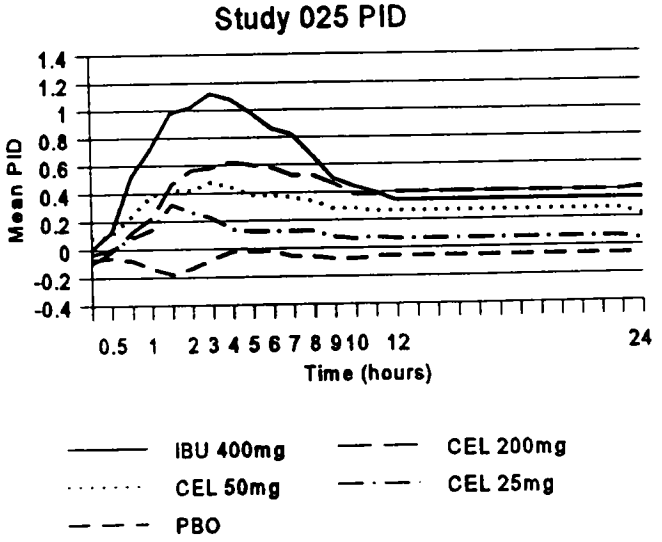


Demographic Summary for PostSurgical Dental Pain Study 49-96-02-025

Reviewer's Results - Study 025	Placebo	Cele 25mg SD	Cele 50mg SD	Cele 200mg SD	Ibuprofen 400 SD
# Enrolled (Safety Evaluable)	50	50	50	50	50
# Completed Study (%)	04 (08%)	04 (08%)	07 (14%)	13 (26%)	08 (16%)
# Req Rescue Meds (%)	46 (92%)	46 (92%)	43 (86%)	37 (74%)	42 (84%)
# Terminations (%)					
- Due to Lost-to-follow-up	0	0	0	0	0
* - Due to Trt Fail/Resc Med	0	0	0	0	0
*- Due to Trt Fail/Resc	46 (92%)	46 (92%)	43 (86%)	37 (74%)	42 (84%)
- Due to Adverse Reaction	0	0	0	0	0
# Pats with Any AE (%)	20 (40%)	23 (46%)	20 (40%)	24 (48%)	23 (46%)
# Pats w Trt-rel AE (%)	07 (14%)	05 (10%)	08 (16%)	09 (18%)	06 (12%)
# Males (%)	21 (42%)	18 (36%)	19 (38%)	17 (34%)	10 (20%)
# Females (%)	29 (58%)	32 (64%)	31 (62%)	33 (66%)	40 (80%)
# Caucasian (%)	27 (54%)	32 (64%)	34 (68%)	27 (54%)	32 (64%)
# Hispanic (%)	18 (36%)	14 (28%)	08 (16%)	17 (34%)	15 (30%)
her (%)	05 (10%)	04 (08%)	08 (16%)	06 (12%)	03 (06%)
Age Range in Years	18 - 38	18 - 46	18 - 45	18 - 46	18 - 50
# Pats Achieving Analgesia	9 (18%)	21 (42%)	23 (46%)	27 (54%)	37 (74%)
# Pats Achieving Perceptible Pain Relief (%)	18 (36%)	29 (58%)	32 (64%)	35 (70%)	41 (82%)

** *Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*

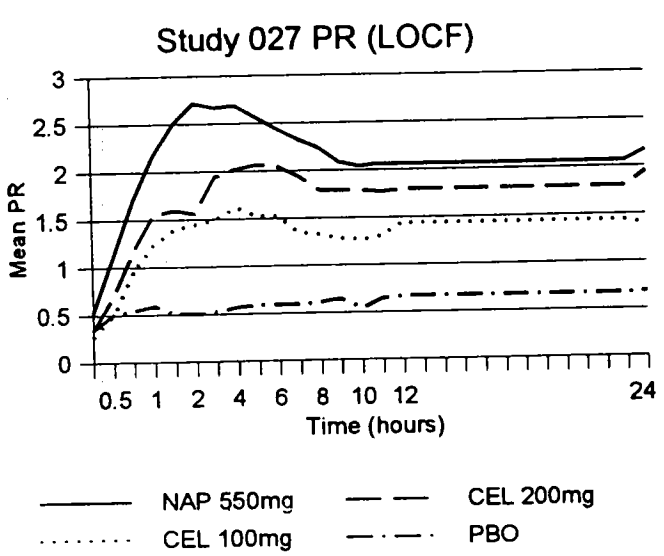


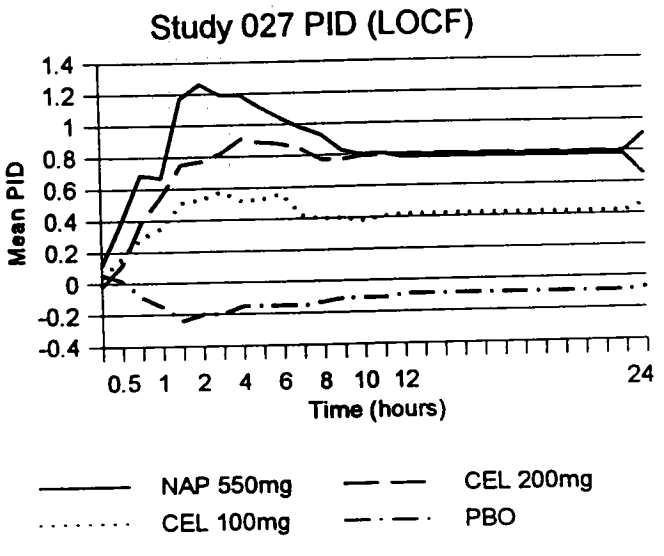


Demographic Summary for PostSurgical Dental Pain Study 49-96-02-027

Reviewer's Results - Study 027	Placebo	Cele 100 SD	Cele 200 SD	Naproxen NA 550 SD
# Enrolled (Safety Evaluable)	55	55	56	54
# Efficacy Eval - ITT (%)	55 (100%)	55 (100%)	56 (100%)	54 (100%)
# Completed Study (%)	09 (16%)	17 (31%)	27 (48%)	28 (52%)
# Req Rescue Meds (%)	46 (84%)	38 (69%)	29 (52%)	26 (48%)
# Terminations - Trt Fail/Resc Med	46 (84%)	38 (69%)	29 (52%)	26 (48%)
# Pats with Any AE (%)	27 (48%)	24 (44%)	29 (52%)	25 (46%)
# Pats w Trt-rel AE (%)	12 (22%)	10 (18%)	14 (25%)	13 (24%)
# Males (%)	25 (45%)	25 (45%)	26 (46%)	24 (44%)
# Females (%)	30 (55%)	30 (55%)	30 (54%)	30 (56%)
# Caucasian (%)	36 (65%)	34 (62%)	39 (70%)	35 (65%)
# Hispanic (%)	05 (09%)	03 (05%)	03 (05%)	01 (02%)
# Other (%)	14 (25%)	18 (33%)	14 (25%)	18 (33%)
# Age Range in Years	18 - 32	18 - 50	18 - 45	18 - 52
# Pats Achieving Perceptible Pain Relief (%)	28 (51%)	38 (69%)	44 (79%)	50 (93%)

** *Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*





Demographic Summary for PostSurgical Orthopedic Pain Study 49-96-02-028

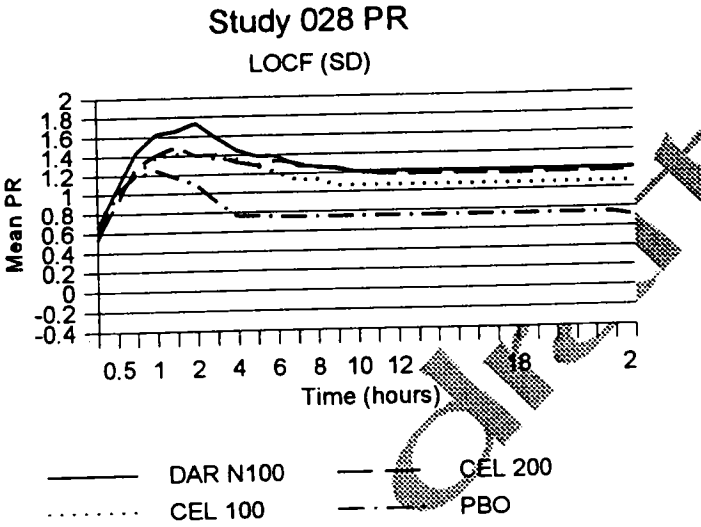
Reviewer's Results - Study 028	Placebo	Cele 100mg BID PRN	Cele 200mg BID PRN	Darvocet N50 (2X) QID PRN
# Enrolled (Safety Evaluable)	60	68	62	65
# Completed Study (%)	01	01	0	01
# Terminations (%)	59 (98%)	67 (99%)	62 (100%)	64 (98%)
- Due to Trt Fail/Resc Med	51	47	43	44
- Due to Adverse Reaction	03	01	09	01
- Due to Noncompliance	03	16	10	19
- Due to Protocol Violation	02	03	0	0
# Pats with Any AE (%)	23	25	25	28
# Pats w Trt-rel AE (%)	16	19	19	21
# Males (%)	30 (50%)	37 (54%)	34 (55%)	36 (55%)
# Females (%)	30 (50%)	31 (46%)	28 (45%)	29 (45%)
# Caucasian (%)	51 (85%)	60 (88%)	59 (95%)	54 (83%)
# Hispanic (%)	02 (03%)	03 (04%)	02 (03%)	03 (05%)
# Other (%)	07 (12%)	05 (07%)	01 (02%)	08 (12%)
# Age Range in Years				

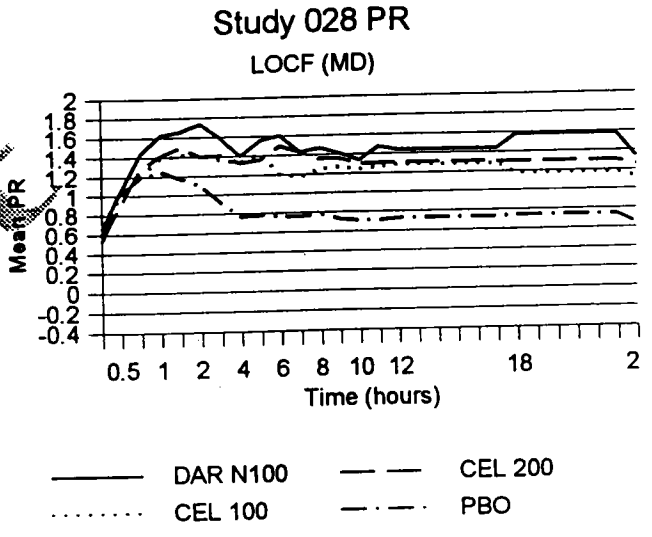
Mean Pain Relief in PostSurgical Orthopedic Pain Study 49-96-02-028

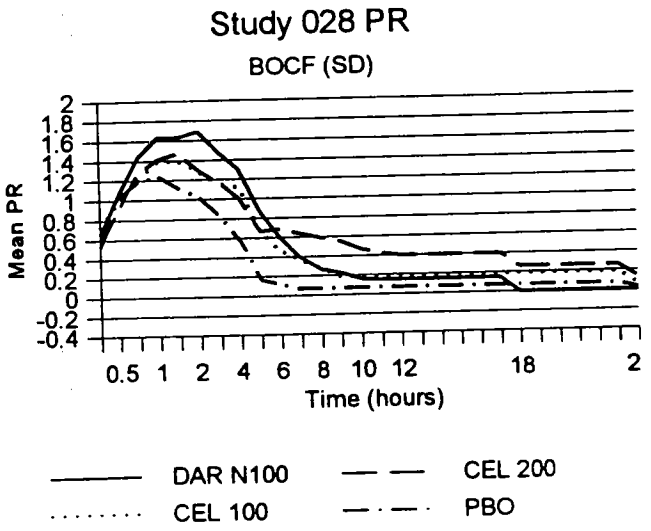
Last Observation Carried Forward (LOCF) - **Single (SD) and Multiple Dose (MD)**
Baseline Observation Carried Forward (BOCF) - **Single (SD) and Multiple Dose (MD)**

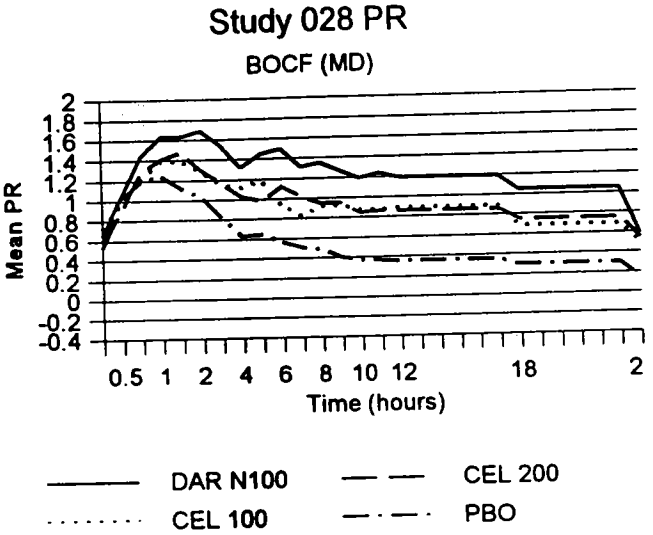
DAR N100 = ***Darvocet N100 QID PRN***
CEL 200 = ***Celecoxib 200 mg BID PRN***
CEL 100 = ***Celecoxib 100 mg BID PRN***

** ***Pain Relief (PR) Scores:*** ***0=none; 1=little; 2=some; 3=lot; 4=complete***





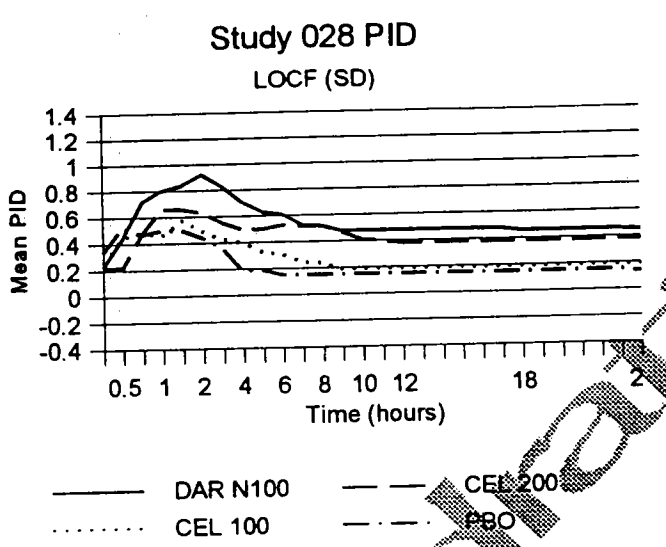


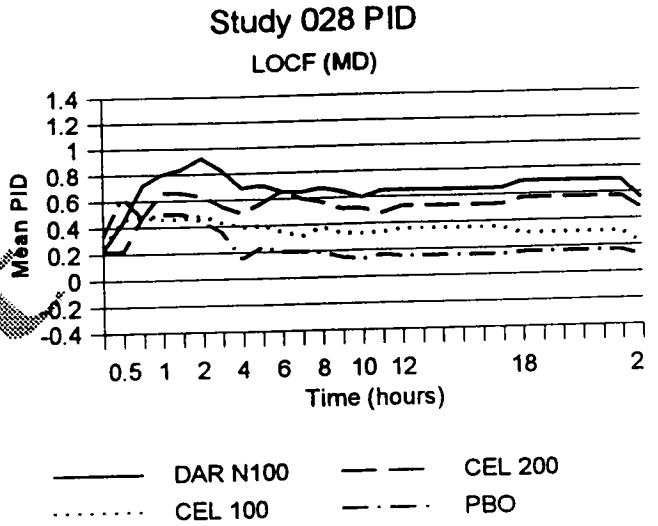


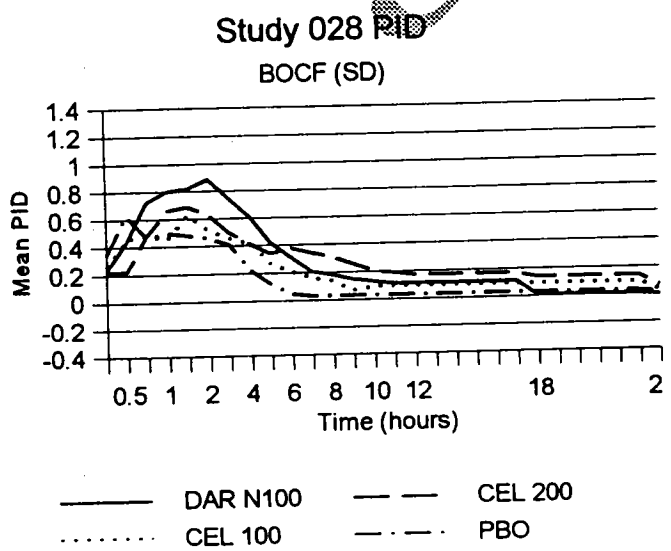
Mean Pain Intenstiy Difference in PostSurgical Orthopedic Pain Study 49-96-02-028

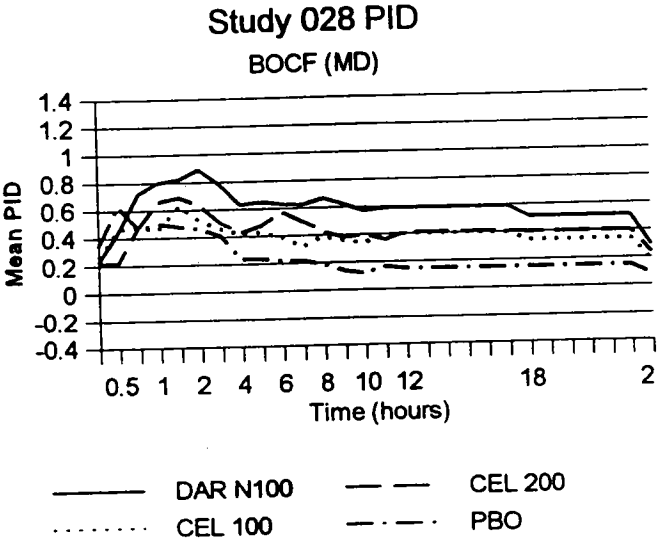
Last Observation Carried Forward (LOCF) - Single (SD) and Multiple Dose (MD)
Baseline Observation Carried Forward (BOCF) - Single (SD) and Multiple Dose (MD)

DAR N100 = Darvocet N100 QID PRN
CEL 200 = Celecoxib 200 mg BID PRN
CEL 100 = Celecoxib 100 mg BID PRN









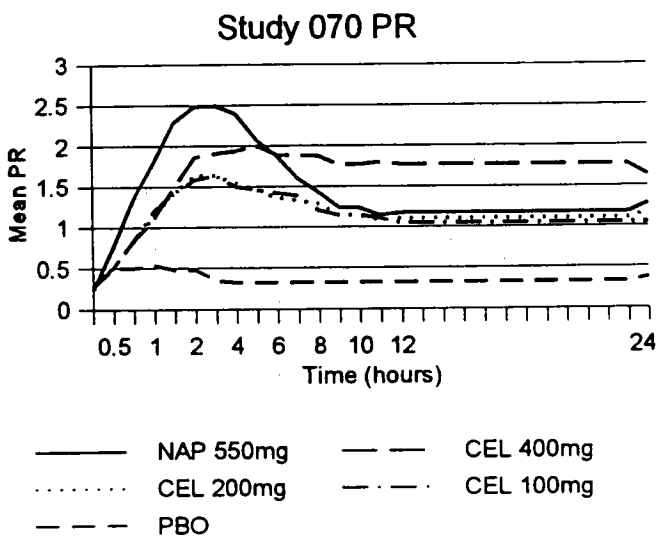
Demographic Summary for PostSurgical Non-Orthopedic Pain Study 49-96-02-029

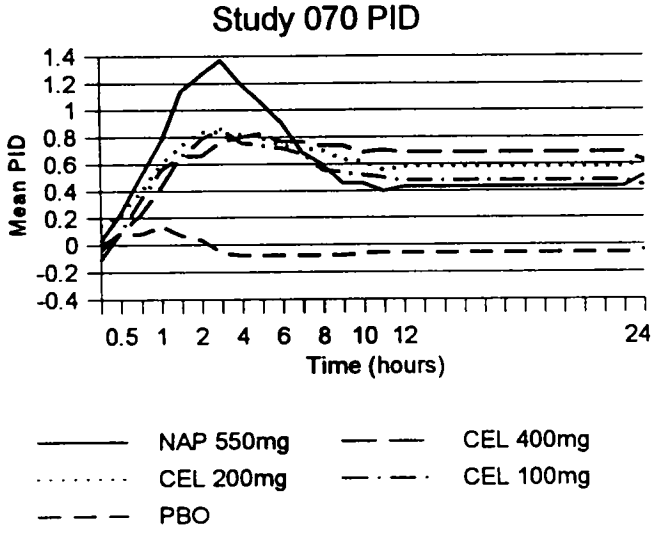
Reviewer's Results - Study 029	Placebo	Cele 100mg BID PRN	Cele 200mg BID PRN	Darvocet N50 (2X) QID PRN
# Enrolled (Safety Evaluable)	40	45	42	40
# Completed Study (%)	1	1	0	0
# Terminations (%)	39 (98%)	45 (98%)	42 (100%)	40 (100%)
- Due to Adverse Reaction	5	2	3	5
- Due to Trt Fail/Resc Med	27	29	28	22
- Due to Noncompliance	5	13	9	13
- Due to Protocol Violation	2	0	2	0
# Pats with Any AE (%)	17 (43%)	20 (44%)	21 (50%)	22 (55%)
# Pats w Trt-rel AE (%)	12 (30%)	20 (44%)	17 (40%)	17 (43%)
# Males (%)	04 (10%)	06 (13%)	07 (17%)	05 (13%)
# Females (%)	36 (90%)	39 (87%)	35 (83%)	35 (88%)
# Caucasian (%)	28 (70%)	40 (89%)	29 (69%)	30 (75%)
# Black (%)	03 (08%)	04 (09%)	09 (21%)	03 (08%)
# Other (%)	09 (23%)	04 (09%)	04 (09%)	07 (18%)

Demographic Summary for PostSurgical Orthopedic Pain Study 49-96-02-070

Reviewer's Results - Study 070	Placebo	Cele 50mg BID PRN	Cele 100mg BID PRN	Cele 200mg BID PRN	Cele 400mg BID PRN	Naproxen 550 QID PRN
# Enrolled (Safety Evaluable)	50	35	50	50	35	35
# Completed Study (%)	50 (100%)	34 (97%)	50 (100%)	50 (100%)	35 (100%)	35 (100%)
# Terminations (%)	0	1	0	0	0	0
- Due to Adverse Reaction	0	1 (#539)	0	0	0	0
- Due to Trt Fail/Resc Med	0	0	0	0	0	0
- Due to Lost-to-follow-up	0	0	0	0	0	0
# Pats with Any AE (%)	24 (48%)	20 (57%)	12 (24%)	18 (36%)	15 (43%)	10 (29%)
# Pats w Trt-rel AE (%)	14 (28%)	8 (23%)	9 (18%)	12 (24%)	5 (14%)	5 (14%)
# Males (%)	20 (40%)	13 (37%)	20 (40%)	20 (40%)	14 (40%)	14 (40%)
# Females (%)	30 (60%)	22 (63%)	30 (60%)	30 (60%)	21 (60%)	21 (60%)
# Caucasian (%)	32 (64%)	18 (51%)	28 (56%)	27 (54%)	23 (66%)	22 (63%)
# Hispanic (%)	13 (26%)	12 (34%)	14 (28%)	16 (32%)	08 (23%)	08 (23%)
# Other (%)	15 (30%)	05 (14%)	08 (16%)	07 (14%)	04 (11%)	05 (14%)

*** Pain Relief (PR) Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete*





Treatment Pairwise Comparisons of Mean Pain Relief (PR) in PostSurgical Dental Pain Studies
Last Observations Carried Forward (LOCF)

LOCF Comparisons	H0.75	H1.0	H1.5	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H24
Study 025															
Ibuprofen 400 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0005	.0008	.0030	.0098	.0398		
Ibuprofen 400 vs Celecoxib 200	.0335	.0020	.0157		.0392										
Celecoxib 200 vs Placebo	.0173	.0012	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0003	.0002	.0009	.0014	.0007	.0004
Study 027															
Naproxen 550 vs Placebo	.0003	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Naproxen 550 vs Celecoxib 200	.0112	.0037	.0037	.0007	.0064	.0149									
Naproxen 550 vs Celecoxib 100	.0019	.0001	.0001	.0001	.0001	.0001	.0003	.0013	.0005	.0013	.0048	.0070	.0078	.0128	.0128
Celecoxib 200 vs Placebo		.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 100 vs Placebo		.0034	.0002	.0002	.0001	.0002	.0009	.0011	.0078	.0115	.0240	.0280	.0220	.0245	.0206
Study 070															
Naproxen 550 vs Placebo	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0010	.0010	.0023	.0016	.0020
Naproxen 550 vs Celecoxib 400	.0245	.0112	.0087	.0117	.0404										
Naproxen 550 vs Celecoxib 200	.0171	.0081	.0021	.0053	.0020	.0057	.0530								
Naproxen 550 vs Celecoxib 100	.0171	.0160	.0021	.0029	.0020	.0038	.0530								
Celecoxib 400 vs Placebo		.0210	.0004	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 200 vs Placebo		.0080	.0003	.0001	.0001	.0001	.0001	.0002	.0001	.0002	.0015	.0011	.0019	.0014	.0026
Celecoxib 100 vs Placebo		.0036	.0003	.0001	.0001	.0001	.0001	.0001	.0003	.0007	.0008	.0011	.0015	.0019	.0103

** *The above are p-values (2-sided testing at alpha level of 5%) for statistically noteworthy comparisons ONLY, i.e. for postdose assessment times of statistically significant differences in mean pain relief between treatment groups (not adjusting for multiplicity of multiple comparisons).*

** *Shaded cells represent statistical significance adjusted for multiplicity (at alpha level of 1.25%).*

Treatment Pairwise Comparisons of Mean Pain Relief (PR) in PostSurgical Dental Pain Studies
Baseline Observations Carried Forward (BOCF)

BOCF Comparisons	H0.5	H0.75	H1.0	H1.5	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H24
Study 025																
Ibuprofen 400 vs Placebo	.0110	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0046	.0216				
Ibu 400 vs Celecoxib 200		.0327	.0019	.0127	.0226	.0257										
Celecoxib 200 vs Placebo		.0184	.0014	.0001	.0001	.0001	.0002	.0003	.0007	.0034	.0029	.0037	.0110	.0140	.0078	.0069
Celecoxib 50 vs Placebo			.0027	.0022	.0079	.0257	.0372									
Study 027																
Naproxen 550 vs Placebo	.0003	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0005
Napr 550 vs Celecoxb 200	.0112	.0051	.0037	.0039	.0005	.0053	.0107									
Napr 550 vs Celecoxib 100	.0019	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0012	.0006	.0020	.0021	.0070	.0057	.0092	.0329
Celecoxib 200 vs Placebo		.0007	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0002	.0007	.0004	.0008	.0010	.0005
Celecoxib 100 vs Placebo		.0195	.0034	.0003	.0002	.0002	.0005	.0025	.0060	.0307	.0501					
Study 070																
Naproxen 550 vs Placebo		.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0011	.0031	.0063	.0063	.0070
Napr 550 vs Celecoxb 400		.0245	.0112	.0055	.0084	.0213						.0449	.0461	.0205	.0259	
Napr 550 vs Celecoxib 200		.0171	.0081	.0019	.0043	.0025	.0046	.0372	.0469							
Napr 550 vs Celecoxib 100		.0171	.0160	.0019	.0019	.0011	.0014	.0168	.0543							
Celecoxib 400 vs Placebo			.0210	.0004	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001	.0001
Celecoxib 200 vs Placebo			.0080	.0002	.0001	.0001	.0001	.0001	.0001	.0002	.0003	.0010	.0032	.0067	.0084	.0123
Celecoxib 100 vs Placebo			.0036	.0002	.0001	.0001	.0001	.0001	.0001	.0002	.0013	.0010	.0032	.0042	.0067	.0315

** *The above are p-values (2-sided testing at alpha level of 5%) for statistically noteworthy comparisons ONLY, i.e. for postdose assessment times of statistically significant differences in mean pain relief between treatment groups (not adjusting for multiplicity of multiple comparisons).*

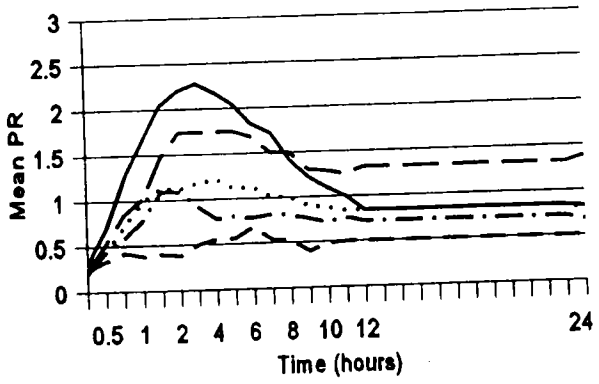
** *Shaded cells represent statistical significance adjusted for multiplicity (at alpha level of 1.25%).*

Mean Pain Relief (PR) in PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

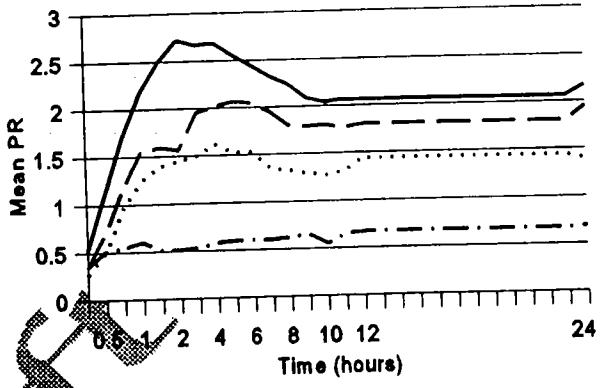
Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Study 025 PR - LOCF



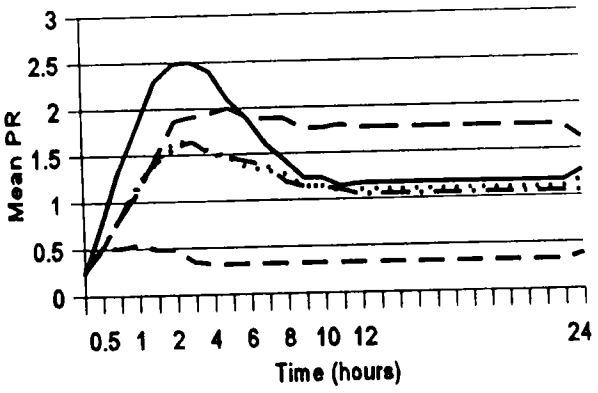
IBU 400mg — — CEL 200mg
CEL 50mg — · — CEL 25mg
— — · PBO

Study 027 PR - LOCF



NAP 550mg — — CEL 200mg
CEL 100mg — · — PBO

Study 070 PR - LOCF



NAP 550mg — — CEL 400mg
CEL 200mg — · — CEL 100mg
— — · PBO

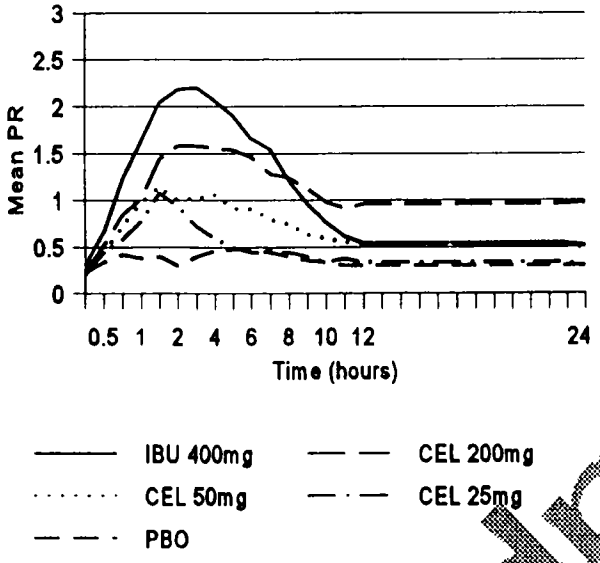
NDA 20-998 Celebrex (Celecoxib) Attachment # 10 B

Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

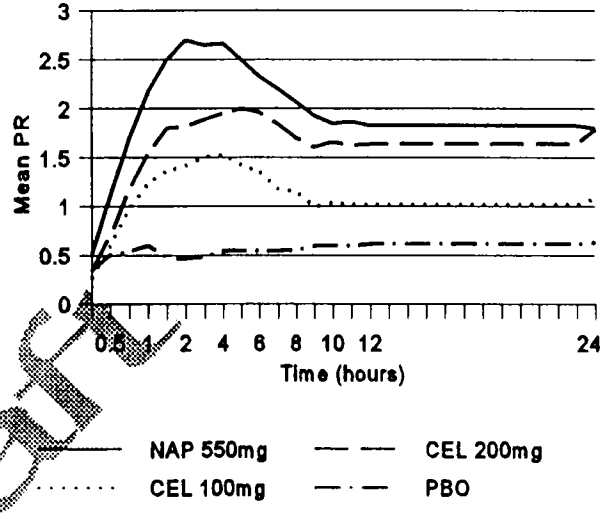
Baseline Observation Carried Forward (BOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

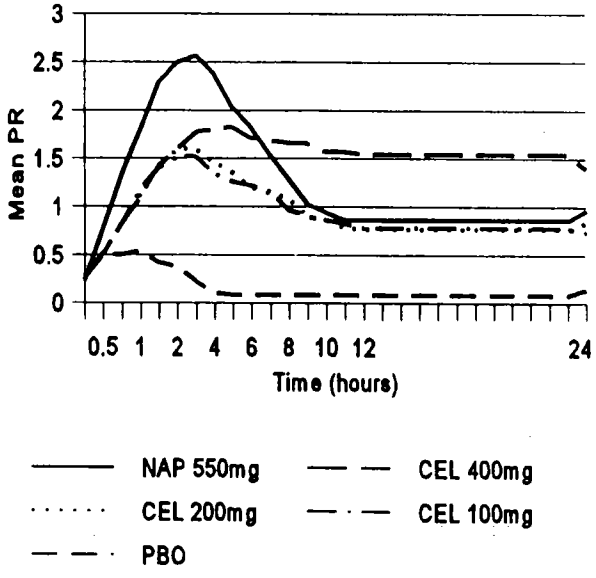
Study 025 PR - BOCF



Study 027 PR - BOCF



Study 070 PR - BOCF



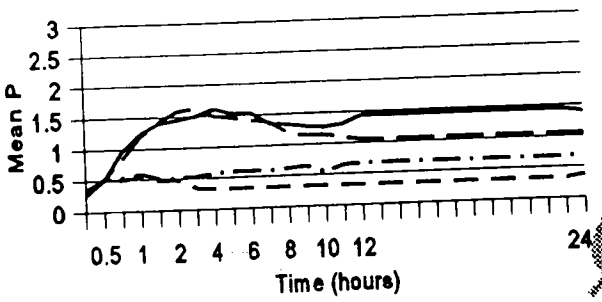
Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Celecoxib 100mg & Placebo - LOCF

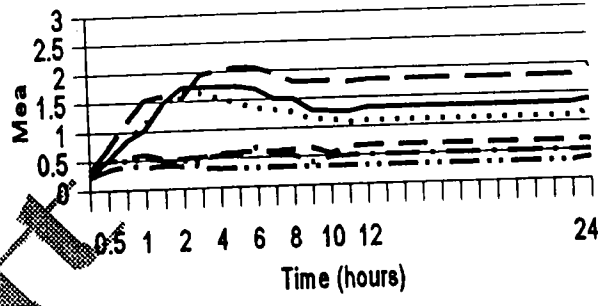
Studies 027 / 070



CEL100(027)
CEL100(070)
PBO(027)
PBO(070)

Celecoxib 200mg & Placebo - LOCF

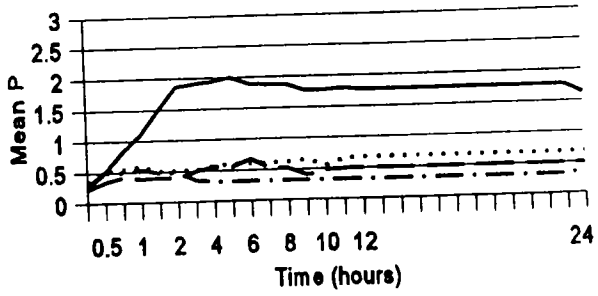
Studies 025 / 027 / 070



CEL 200(025)
CEL 200(027)
CEL 200(070)
PBO(025)
PBO(027)

Celecoxib 400mg & Placebo - LOCF

Studies 025 / 027 / 070



CEL400(070)
PBO(025)
PBO(027)
PBO(070)

APPEARS THIS WAY
ON ORIGINAL

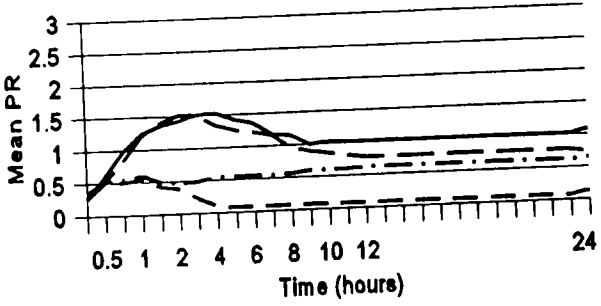
Mean Pain Relief (PR) Summarized by Dose PostSurgical Dental Pain Studies

Baseline Observation Carried Forward (BOCF)

Pain Relief Scores: 0=none; 1=little; 2=some; 3=lot; 4=complete

Celecoxib 100mg & Placebo - BOCF

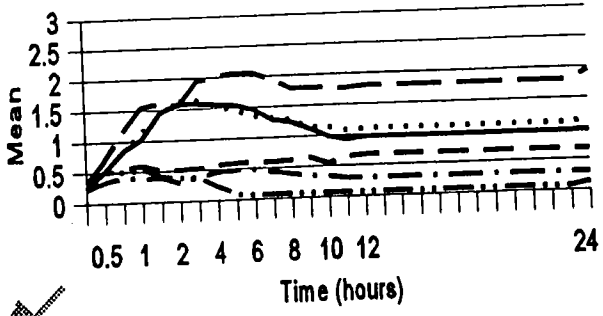
Studies 027 / 070



CEL100(027)
CEL100(070)
PBO(027)
PBO(070)

Celecoxib 200mg & Placebo - BOCF

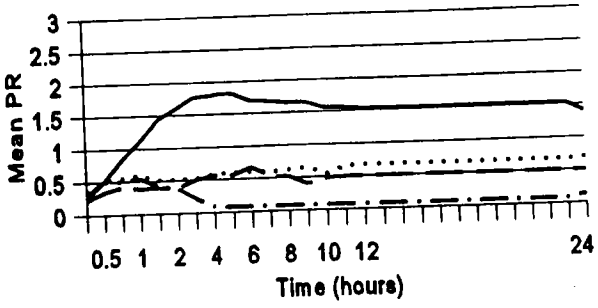
Studies 025 / 027 / 070



CEL 200(025)
CEL 200(027)
CEL 200(070)
PBO(025)
PBO(027)

Celecoxib 400mg & Placebo - BOCF

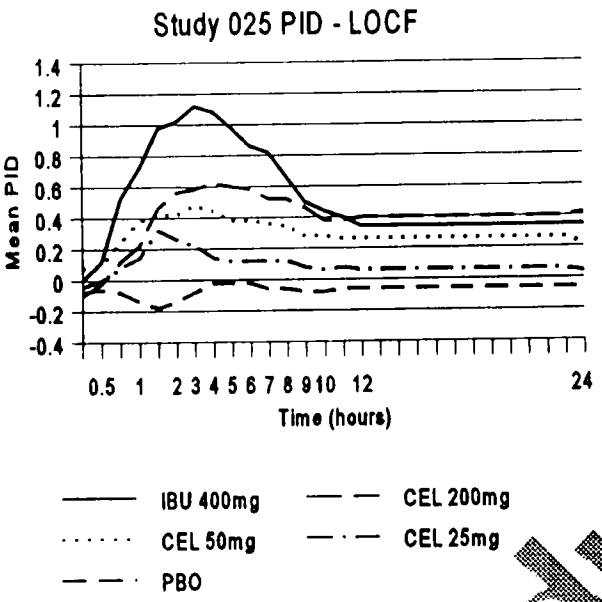
Studies 025 / 027 / 070

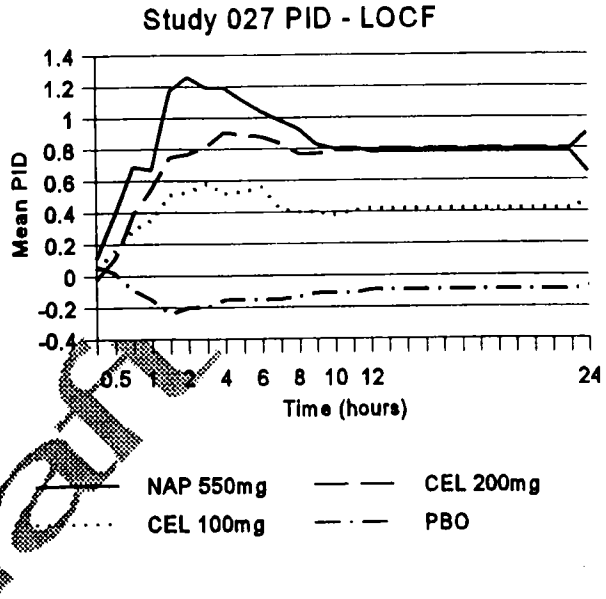


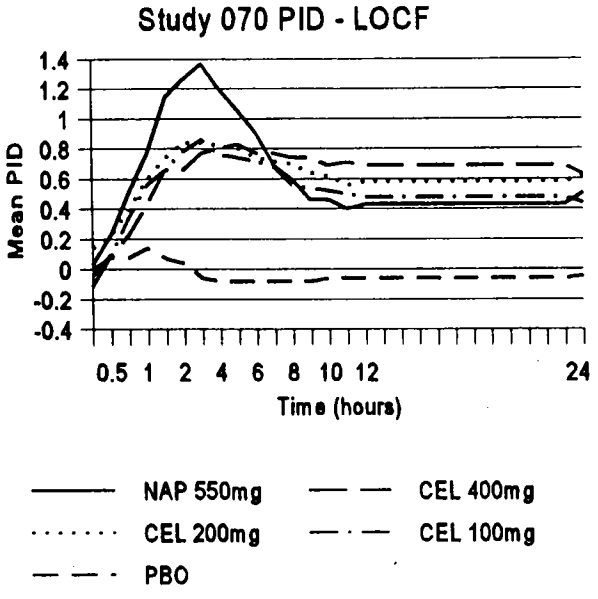
CEL400(070)
PBO(025)
PBO(027)
PBO(070)

Mean Pain Intensity Difference (PID) in PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)

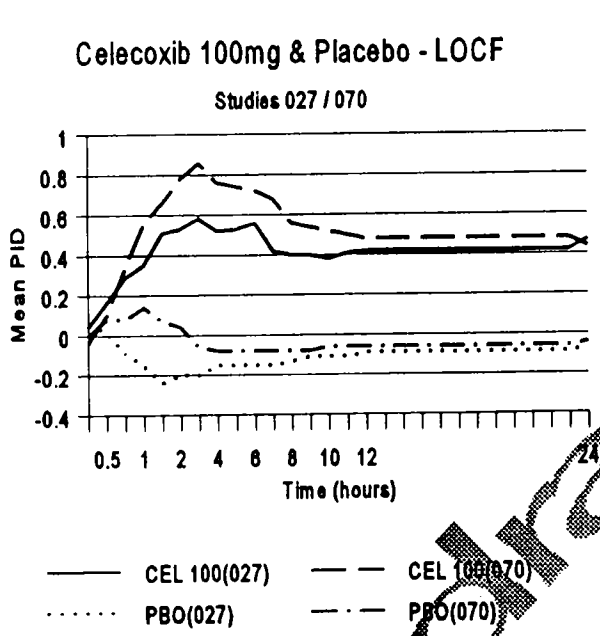


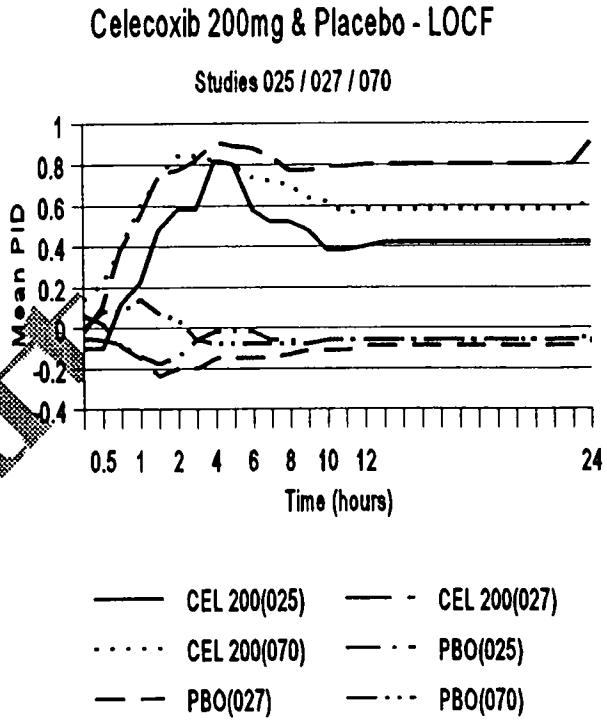


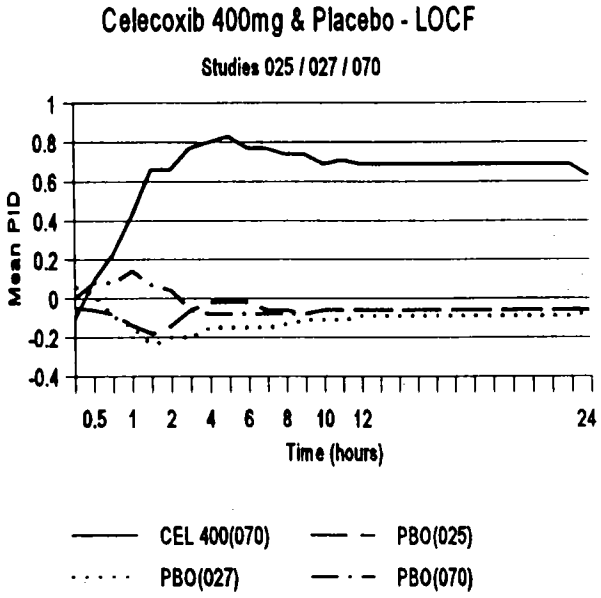


Mean Pain Intensity Difference (PID) Summarized by Dose PostSurgical Dental Pain Studies

Last Observation Carried Forward (LOCF)



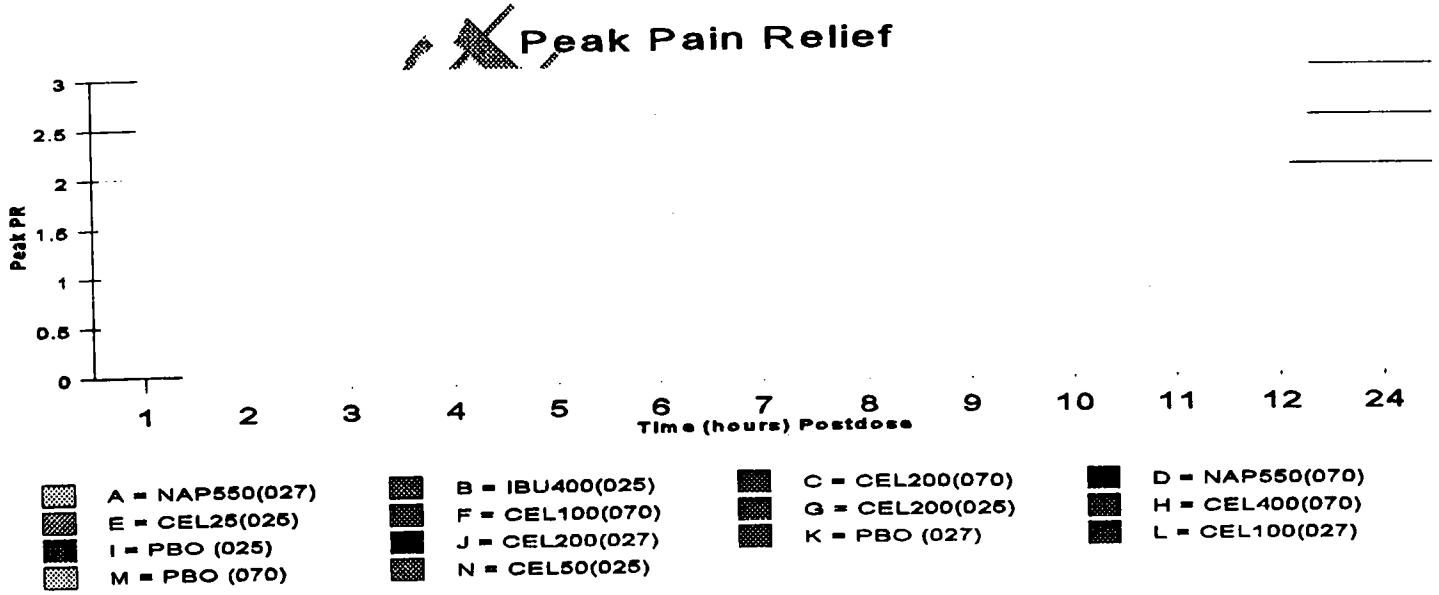




Dose Level Summary of Mean and Peak Pain Relief (PR) in PostSurgical Dental Pain Studies
Baseline Observations Carried Forward (BOCF)

Study	Celecoxib 25	Celecoxib 50	Celecoxib 100	Celecoxib 200	Celecoxib 400	Ibuprofen 400	Naproxen 550
025 PR Onset	H0.75 ---> H3	H1 ---> H2		H1 ---> H24		H0.5 ---> H8 (PBO) H0.5 ---> H8 (25/50) H0.5 ---> H4 (200)	
PR Peak (hour)	1.1 at H2	1.22 at H4		1.74 at H2		2.28 at H3	
027 PR Onset			H1 ---> H6	H0.75 ---> H4			H0.5 ---> H24 (PBO) H0.5 ---> H24 (100) H0.5 ---> H4 (200)
PR Peak (hour)			1.62 at H4	2.07 at H4			2.72 at H2
070 PR Onset			H1 ---> H12	H1 ---> H24	H1.5 ---> H24		H0.75 ---> H24 (PBO) H0.75 ---> H8 (50) H0.75 ---> H4 (100/200) H0.75 ---> H3 (400)
PR Peak (hour)			1.64 at H3	1.64 at H2	1.94 at H4		2.6 at H3

*** "Onset Hx ---> Hy" is Time (Hour x through y) of Statistically Significant Differences in Mean Pain Relief from that of Placebo.*
"Peak at Hour x" is Peak Pain Relief Score Attained at Hour x.



Onset and Duration of Statistically Significant Differences in Mean Pain Relief (PR)

PostSurgical Dental Pain Studies

Baseline Observations Carried Forward (BOCF)